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TRAUMATIC OSTEOMYELITIS OF THE CRANIAL VAULT

WITH PARTICULAR REFERENCE TO PATHOGENESIS AND TREATMENT

LEO J. ADELSTEIN, M.D.
Junior Attending Neurosurgeon, Los Angeles County General Hospital
AND
CYRIL B. COURVILLE, M.D.
Resident Neurosurgeon and Neuropathologist, Los Angeles County General Hospital
LOS ANGELES

Osteomyelitis of the bones of the skull occurs most commonly as a result of inflammatory conditions in the accessory nasal sinuses. Infection of the frontal bone following operative procedures on the frontal sinus has been made the subject of numerous case reports and of several extensive treatises on its etiology, pathology and treatment. Osteomyelitis of the maxilla following antral infections is more rare. True osteomyelitis of the petrous bone and the adjacent occipital bone following disease of the middle ear is probably still more rare, because of the anatomic characteristics of the bone itself.

Traumatic osteomyelitis of the cranial vault has been given but little attention in the now extensive literature dealing with craniocerebral injuries. Could a complete list of such cases be compiled from all sources, it would be considerably more impressive, for individual cases must be more common than might be supposed from a review of the literature. As we have had six cases come to our attention in a series of more than five thousand cases of injury to the head on the neurosurgical service of this hospital, it is our purpose to consider its etiology, pathogenesis and clinical course, and to attempt to deduce therefrom a rational method of treatment. While in some of the cases reported the occurrence of infection is somewhat in the nature of a confession, it has seemed worthwhile, nevertheless, to record our observations.

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From the Neurosurgical Service of Dr. Carl W. Rand, and the Neuropathological Laboratory, Los Angeles County General Hospital.

Dr. Adelstein has followed most of the cases presented herewith through their long clinical course, and has elaborated the plan of treatment. Dr. Courville is responsible for the proposed classification of the condition, based on roentgenologic studies, and the discussion of its pathogenesis and pathology. Dr. Ray A. Carter, of the Department of Roentgenology of the hospital, supplied the roentgenograms illustrating the article.

HISTORICAL NOTE

It is probable that secondary infections of the bones of the skull following injury to the scalp and skull have been observed from earliest times. In spite of the great increase in the number of cases of injuries to the head, the present relative rarity of infections of the bones is to be attributed to the modern prompt and careful treatment of superficial wounds which tend to heal if given an opportunity. A study of the historical references to this condition gives one some insight as to the progress of our knowledge of it. Hippocrates,[1] in his essay "On Injuries of the Head," referred to the extension of the infectious process to the bone from the infected scalp. The principles of treatment of wounds of the head underwent little change through the following centuries as far as the prevention and cure of the infections themselves were concerned. Little is recorded except case reports from the fifteenth to the eighteenth centuries. Percival Pott[2] drew attention to the fact that necrosis and infection of the skull followed local traumatisms. He described two forms of the condition: (1) a localized bony necrosis on which inflammation was engrafted, and probably due to the actual implantation of infectious material in the outer table of the skull through an open wound, and (2) a local necrosis and suppuration with the overlying scalp intact. The latter condition has become known in the surgical literature as "Pott's puffy tumor." His treatment of the inflammatory lesion of the bone was a free removal of bone, especially when pus was present over the dura. Bell,[3] like Pott, was of the opinion that the source of the trouble lay in the separation of the periosteum from the bone, depriving the latter of its blood supply. He also described local suppuration of bone without superficial wounds, and recommended extensive removal of the diseased bone.

Abercrombie[4] described the findings in cases of inflammation of the cranial bones collected from the literature up to his time. In some cases the lesion followed injury, but in none of these was the typical sequence described in which the infection followed open wounds.

With the improvement in the treatment of contaminated scalp wounds with antiseptics and removal of foreign material, secondary osteomyelitis of the skull has become a rarity. In an extensive treatise on injuries of the head, Rawling[5] made no mention of secondary

1. Hippocrates: The Genuine Works of Hippocrates, translated by Francis Adams, London, Sydenham Society, 1849, vol. 1, pp. 454, 460, 461 and 463.

2. Pott, Percival: Chirurgical Works, London, T. Lowndes, 1783, vol. 1, p. 44.

3. Bell, Charles: A System of Operative Surgery Founded on the Basis of Anatomy, London, Longman, Hurst, Rees & Orme, 1807, vol. 1, p. 416.

4. Abercrombie, John: Pathological and Practical Researches on Diseases of the Brain and Spinal Cord, ed. 3, London, Waugh & Innes, 1834, p. 179.

5. Rawling, L. B.: The Surgery of the Skull and Brain, London, Oxford University Press, 1912.

osteomyelitis of the skull. Most modern treatises on surgery are content to advise the removal of gross contaminating material and the use of antiseptics in the prevention of infection, and do not give any description of the condition itself.

ANATOMIC FACTORS

In order to approach the problem of osteomyelitis of the cranial vault properly, it is necessary to review briefly the essential anatomic factors that favor the admission and spread of infection. The rarity of the condition with adequate treatment of open wounds, even in the presence of compound comminuted fractures, speaks well for the natural local defense against such infections. The anatomic factors that need to be elaborated on may be summarized as (1) the character of the bone, (2) its arterial supply and (3) its venous drainage.

Character of Bone.—The cranial vault is formed by the frontal, two parietal, the occipital and the squamous portions of the temporal bones. These bones or portions of bones are composed of two compact layers, a thick and somewhat elastic outer table and a thinner and more brittle inner table, between which a thin layer of cancellous bone, or diploe, is interposed. The internal and external surfaces have a punctate appearance, owing to the points of entrance of fine blood vessels. This is particularly true of the inner table, for the main source of the blood supply of the vault is from the meningeal arteries. This surface is also more irregular, owing to the convolutional markings, the points of special dural attachment and the openings of the emissary veins.

The firmness and thickness of the outer table prevent the ingress of infection when the bone has been exposed by injury even after the periosteum has been scraped off. Were it not for this, osteomyelitis of the skull would undoubtedly be of common occurrence in injuries in which the subaponeurotic space has been opened and infected.

Arterial Supply.—The cranial vault has a double blood supply; a minor external one derived from the small arterioles of the pericranium, especially in the regions of muscle attachments, and a major internal one derived from the meningeal arteries in the dura. The latter consists essentially of the terminal distribution of the middle meningeal arteries, the large size of which indicates that they have a more important function than that of supplying the fibrous dura alone, as Jefferson and Stewart[6] have emphasized. The points of entrance of the terminal arterioles into the inner surface of the bone give it a finely punctate appearance.

It has been a tradition handed down from the time of Percival Pott, that a factor in the production of necrosis is the separation of the over-

6. Jefferson, G., and Stewart, D.: On the Veins of the Diploë, Brit. J. Surg. **16**:70, 1928.

lying pericranium and underlying dura from a given portion of bone, therefore depriving it of its blood supply. That this is not necessarily the case is the experience of surgeons who have dealt with cranial injuries. In an originally clean, or even in potentially infected, wounds that have been carefully antisepticized, loosened fragments of bone will usually grow and aid in the filling of a defect. Such fragments, of course, are more susceptible to infection, should it develop in a wound, and usually sequestrate, as we shall subsequently show.

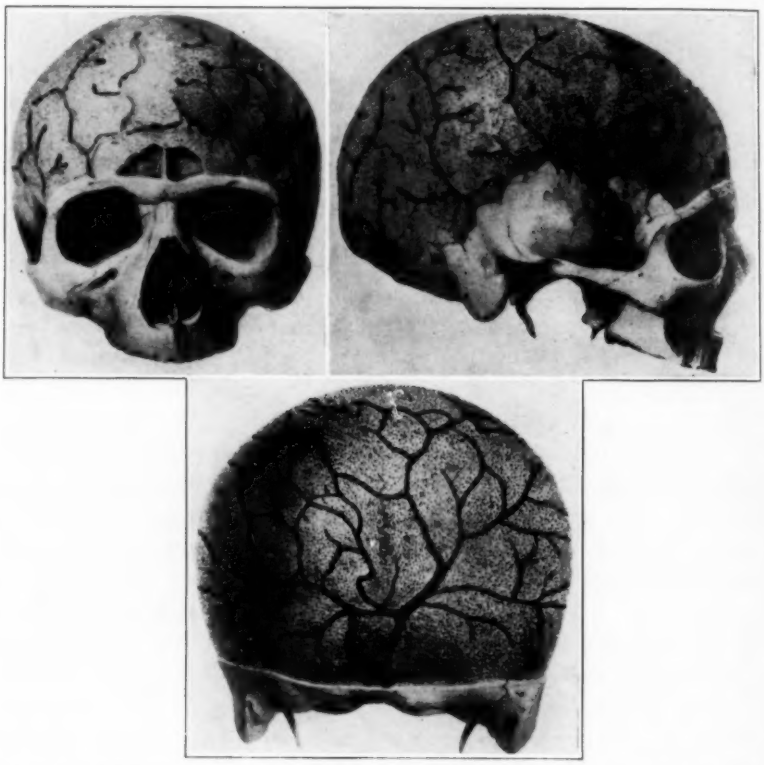

Fig. 1.—Arrangement of the diploic veins in the cranial vault. (After Breschet: Recherches anatomiques, physiologiques et pathologiques sur les canaux veineux des os, 1830.)

Venous Drainage.—The bones forming the cranial vault are drained by an internal system of comparatively large, thin-walled channels in the diploe. In infancy and childhood, these veins form a separate system within the individual bones, but as age advances and ossification of the suture lines takes place, the various systems join to become more or less continuous. In later adult life, these channels are often found to be enlarged and are commonly visible in roentgenograms. There are

three sets of veins on either lateral half of the skull, the frontal, the parietal (consisting of the anterior and posterior temporal veins) and the occipital, draining the bone thus designated (fig. 1). Each group forms a V, with its apex downward. The frontal system drains into the supra-orbital vein, usually in the supra-orbital notch. The antero-temporal vein drains into the sphenoparietal sinus, and the postero-temporal vein into the lateral sinus. The occipital system drains either internally into the lateral sinus or externally into the occipital vein of the scalp. The venous drainage is therefore in a direction opposite to its arterial supply, which comes by way of the anterior and middle meningeal arteries.

In roentgenograms of the skulls of adults, there is frequently seen a network of large diploic veins in the posteroparietal region, which forms the typical "spider" arrangement. This is due to the larger size of the posteroparietal channels, and to their abundant connections with the occipital group. In addition to the progressive enlargement of these channels with advancing age, there are also formed direct communications between the diploic veins and the terminations of the meningeal vessels, probably due to a gradual erosion of the floor of the arterial grooves. These communications may serve as points of entrance of infections into the diploic spaces.

PATHOGENESIS

It was an object of this investigation to study the pathology of osteomyelitis in order to determine the rationality of a plan of treatment that had been elaborated and used with reasonable success. We were denied the privilege of studying either the surgical or the postmortem pathologic changes, because the plan of treatment was essentially nonoperative, and none of the patients died. Therefore, in an investigation of pathogenesis, it was necessary to rely on the clinical course of the disease, information gained from repeated roentgenologic examinations and a study of an occasional sequestrum recovered from the draining wound. From these sources of information an attempt has been made to portray the sequence of events that lead to healing of the infection.

Mode of Entrance of Infecting Organism.—There are a variety of ways in which the offending organism gains entrance to the bone, and one may more or less accurately foretell from its mode of invasion the course of the condition, should osteomyelitis develop. In local bruises with or without open wounds, infection is presumably introduced by the traumatic agent, or comes from infected hair follicles. In closed wounds, it may at times be blood borne. Infection may be introduced into the bone when the outer layer has been ground off by scraping or

glancing wounds, often with irregular tearing or avulsion of the overlying scalp. This was the source of the infection in case 3 of our series. In one case (case 4) an operative decompression site for the removal of a subdural clot became secondarily infected from the original adjacent wound in the scalp, with consequent extensive osteomyelitis of the skull. Another common mode of invasion is the development of frank infection in a compound comminuted fracture of the skull, either immediately, or after a latent interval. In another case (case 5) the infection developed after an interval of several weeks, the organism evidently being of a low degree of virulence. As a final possible method of invasion, we find a rather unusual sequence of events in case 6, in which a comminuted depressed fracture of the parietal region was sustained by a fall from a moving automobile. An operation was performed and the depressed fragments elevated. The wound healed by first intention. The child was prone to develop staphylococcus infections of the skin, and some days after the operation numerous small pustules developed over the scalp. Two of these, which were deeper than the rest, resulted in abscesses of the scalp which extended through into the subaponeurotic space, possibly at the site of former bruises. The underlying fragments became secondarily infected and finally sequestrated.

Course of Infection.—The mode of entry of the infecting organism is largely responsible for the lesion produced. Because of the characteristic appearance in the roentgenogram, traumatic osteomyelitis of the skull may be classified as follows:

1. Localized osteomyelitis:
   (*a*) Sclerosing osteitis:[7]
      (1) Following an open wound of the scalp (Pott's first type of infection of the skull)
      (2) Following local injury but with the scalp intact ("Pott's puffy tumor")
   (*b*) Circumscribed osteomyelitis:
      Following direct implantation of infection into the diploe by abrasion of the outer table.
2. Spreading osteomyelitis:
   Following invasion of the diploic venous channels from a fracture line or operative defect
3. Infectious necrosis of fragments in comminuted skull fracture:
   Direct or indirect infection of the fragments from a contaminated overlying wound or a secondarily infected operative wound.

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7. It was decided to indicate the two local variations as osteitis and osteomyelitis. In local osteitis, the sclerosing reaction is essentially one of the bony tables, although the diploe are incidently involved. In circumscribed osteomyelitis the infection is primarily in the diploic spaces rather than in the bone.

Classifications are apt to be incomplete and often imperfect, but the foregoing one seems to answer the purpose so far as our own experience goes. The developmental stages of each type will be considered in turn.

Localized Osteomyelitis.—Under this heading have been included all types of traumatic osteomyelitis which remain as a purely local lesion. They are a response to an ingress of infectious material, which results in a local inflammatory reaction that heals by a sclerotic process, the degree of which depends on the extent of the original invasion.

In sclerosing osteitis of the skull, so well described by Pott, there is an original focus in the bone which is, or becomes, infected, from which the spread is limited. The essential difference in the two varieties is that of the exact means of infection. In the first, the instrument of trauma which cuts the scalp injures the surface of the bone and infects it. The infectious material in this case is therefore inoculated directly into the bone itself. No such case occurs in our series, unless, perchance, in case 2 a superficial wound was present following the blow on the head. In the second type, known as "Pott's puffy tumor," the injury, again caused by a localized application of force, creates an area of lowered resistance but does not of itself carry in the infectious material. This is often the result of a comparatively minor injury, and the patient may give little or no attention to it at the time. After a variable interval, about a week each in our two cases (cases 1 and 2), a tender, fluctuant swelling develops, which may be incised surgically, or may rupture spontaneously with the discharge of pus. The infecting organism is likely derived from the hair follicles in the overlying scalp, released by the injury, but may be brought to the focus by the blood stream.

In either case, a usually avirulent infection is engrafted on a more or less extensive necrotizing focus at the point of injury. There is an almost coincident development of the protective reaction and the infection, so that the process soon reaches an equilibrium, and there is no further spread of the infection. As a result of a recent surgical experience,[8] it has been learned that there is an active vascular reaction in a

8. Since this paper was read, we have had the opportunity to study the case of an addtiional patient recently admitted to this hospital. A 59 year old Caucasian man had been injured in an automobile accident on Jan. 1, 1932, sustaining a laceration of the scalp in the left parietal region, a basal fracture of the skull and multiple fractured ribs, with contusion of the lungs. Three and a half months after the injury, a fluctuant and tender swelling of the scalp appeared in the left parietal region at the site of the former laceration. This was incised by an attending physician, with profuse drainage of pus. The wound continued to drain in quantities, and as osteomyelitis was suspected, the patient was sent to the hospital on May 9, 1932, for care. Roentgenograms of the skull revealed an area of mottling about the size of a quarter in the left posterior parietal region.

fairly wide zone about the infected area, though in most cases the infectious process becomes limited in extent. The factors that determine the limits of the spread of the infection are the virulence of the infecting organism, the resistance of the local tissues, as well as the immunologic reaction of the body, and the nature of the minute anatomy of the region thus involved. For instance, if the focus were immediately over a diploic vessel, the lesion might be somewhat elongated, as was apparently the situation in both of the cases of the type in this series (cases 1 and 2). It is not usually a question of a purely peripheral expansion from a central focus, but rather the isolation of a central mass of bone by an encircling process with the ultimate formation of a sequestrum. Healing occurs with the formation of sclerosed bone at the margin of the defect with some variable degree of proliferation of new bone. It is this formation of bone which gives rise to the typical roentgen picture of an increased density of the bone about the defect. The healing process is slow, often a matter of months, with continuous drainage from the overlying sinus in the scalp.

As has been stated, the lesion is likely to remain a local one throughout its course. In case 2, in the adjacent right parietal region, there were found two adjacent areas of rarefaction which were suspected of being extensions (metastases) from the original focus. However, these areas remained more or less unchanged, and at least did not break down, and may have been unrelated lesions. There was no history or evidence of syphilis in the patient. It is theoretically possible for such secondary foci to occur, although we have not had occasion to recognize them with certainty.

The term *circumscribed osteomyelitis* has been retained for another localized type of inflammation. In such cases the infectious material is ground into the diploe with abrasion of the outer table as the result of glancing blows or of scraping the head along the roadway. About each of the infected particles a local infection arises, so that numerous

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While the patient was under treatment right hemiparesis developed rather suddenly, and a few hours later, right-sided jacksonian convulsions made their appearance. As an intracranial extension of the infection was suspected, the area was explored, and a localized extradural abscess was found beneath the area of bone necrosis. Another exploration was carried out two days later because the jacksonian convulsions persisted. A localized, encapsulated, subdural abscess was exposed and drained. The patient died in a few days of a septic meningitis.

Of special interest to us was the condition of the diseased bone. Entirely separated from the adjacent outer table and the underlying diploe was an elongated sequestrum. The surrounding bone and underlying inner table were soft and friable, and when dry, the outer surface of the adjacent skull had a yellowish appearance as though the bone were dead. For a fairly wide zone (about 5 cm.) about the original focus, the outer table "wept" blood, owing to the increased vascularity of the underlying diploic spaces. This was also demonstrated by the profuse bleeding from the opened diploic spaces.

small purulent foci develop. The abraded area becomes involved diffusely first by a confluence of the smaller areas and then by a spread of the process into the adjacent diploe. The outer and inner tables in the regions thus invaded may not be involved, and the only indication of diploic invasion may be a typical mottling as seen in the roentgenogram. Healing occurs by only a minor degree of sclerosis, less marked than in the cases of sclerosing osteitis. Invaded areas of diploe become less mottled and fade away, according to subsequent roentgenograms in our case. If the inner table sequestrates, proliferation from its deeper margins reduces the size of the remaining defect. This regeneration of bone is evidently due to a greater healing activity of the inner table.

In *spreading osteomyelitis* of the skull, the infection begins at a fracture line in the skull, or at the margin of an operative defect (as a decompression opening). It travels along the opened diploic channels, usually in a retrograde direction of the venous flow, i. e., toward the vault rather than the base. This is likely accounted for by stasis of blood in the diploic channels with resulting thrombosis, followed by a retrograde spread of infection, either in the venous channels themselves, or in the diploic spaces about them. When such spaces are followed until two meet, a sequestrum is outlined, being visualized in the roentgenogram by the enlargement and prominence of such spaces. Extension through the inner and outer table from this enlarged channel converts this area into a free sequestrum.

In the third type of traumatic osteomyelitis, infection is superimposed on a comminuted fracture. The process in such cases is fortunately limited by the fracture lines about the fragments; at least, this was what occurred in the cases in our series. Had infection started before reparative processes had begun in the fracture lines of the bones, invasion of the diploic spaces and vessels might have occurred, and a different picture might have been presented. We have as yet seen no such case, but the possibility must be admitted. The process is limited in the surrounding bone, probably by a prompt and active response to the infection. The fragments already separated from their blood supply are more susceptible to the necrosing process, and in fact soon become sequestrums in which degeneration takes place. In one of our cases infection began after fibrous union of the fragments with the adjacent bone had already started.

Formation of Sequestrums.—In any type of traumatic osteomyelitis, sequestrums are likely to be formed. They are often discharged spontaneously, especially if of small size. At times it may be necessary to remove larger ones surgically. The method of formation of sequestrums, as well as their ultimate fate, differs in the various types of osteomyelitis and will be considered separately.

In sclerosing osteitis, although the original necrosis and infection are essentially focal, an elongated sequestrum is usually formed and discharged. This would lead one to the conclusion that the infectious process had spread around and isolated a central island. If this spread occurs in the diploic spaces themselves, one wonders why it is so limited in extent. Furthermore, the sequestrum is elongated, and often remains attached to the adjacent skull by a pedicle at either end, usually toward the base and the vault of the skull. This is evidence that the infection does not spread concentrically and diffusely, but longitudinally and more or less parallel. It may take place along small venous radicals in the diploe.

In circumscribed osteomyelitis, the sequestrum usually consists of fragments of the inner table beneath the abraded area. As shown in our case, the inner table beneath the eroded area becomes isolated by a ring of rarefaction necrosis. This rounded sequestrum may in turn be broken up and discharged. A still different situation exists in spreading osteomyelitis. As shown in our case, the sequestrum is outlined by the infection spreading along the diploic veins, to be separated entirely later when the outer and inner tables over the infected channels become eroded. Invasion of the diploic spaces of the sequestrum then occurs, with more marked destruction of the outer than the inner table. Possibly because of its more abundant blood supply, the inner table escapes except for the erosion of its margins. The conception necessitates a continued attachment of the "sequestrum" to the underlying dura for a variable period following its peripheral detachment. This island of bone becomes, in fact, a sequestrum only when this connection with the dura has been broken. Figures 2 and 3 illustrate the change taking place in the sequestrum in case 4.

When infection occurs in a case of compound comminuted fracture of the vault, particularly before fibrous union has taken place, practically all of the smaller fragments will become infected and form sequestrums. In case 6, one of the larger fragments, being more distantly situated from the source of infection, escaped the process and remained attached to the adjacent skull. Before discharge, a variable degree of necrosis takes place in all sequestrums. In contrast to what occurs in sequestrums secondary to spreading osteomyelitis of the skull, the inner table of such fragments undergoes a greater degree of necrosis than the outer table (fig. 4). This is likely due to the active invasion of the minute perforations of the inner table, points of entrance of the terminal arteries. The outer and more solid surface is less exposed to invasion of the infectious organism.[8a]

8a. Destruction of the inner and outer bony tables does not occur to an equal degree, differing as to both the extent and the table most markedly involved. Cushing (Keen, W. W.: Surgery, Philadelphia, W. B. Saunders Company, 1912, vol. 3,

(*Footnote continued on page 550*)

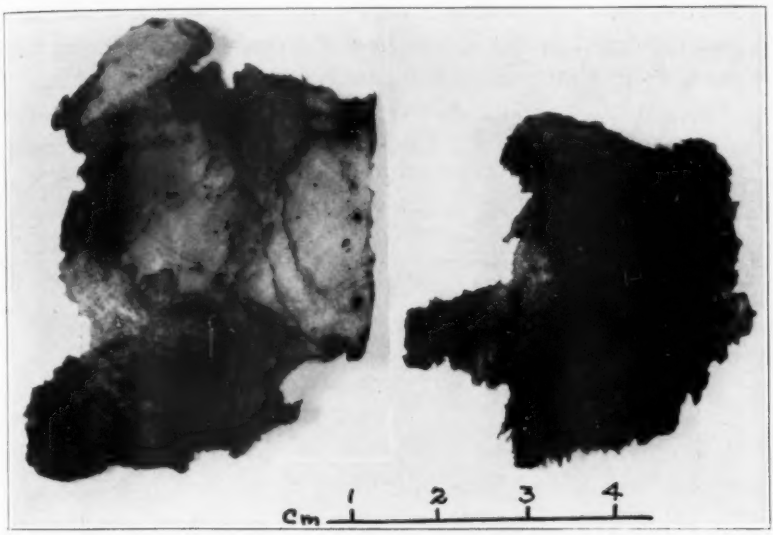

Fig. 2 (case 1).—Sequestrums, showing marked erosion of the outer table which has been completely destroyed on the smaller fragment.

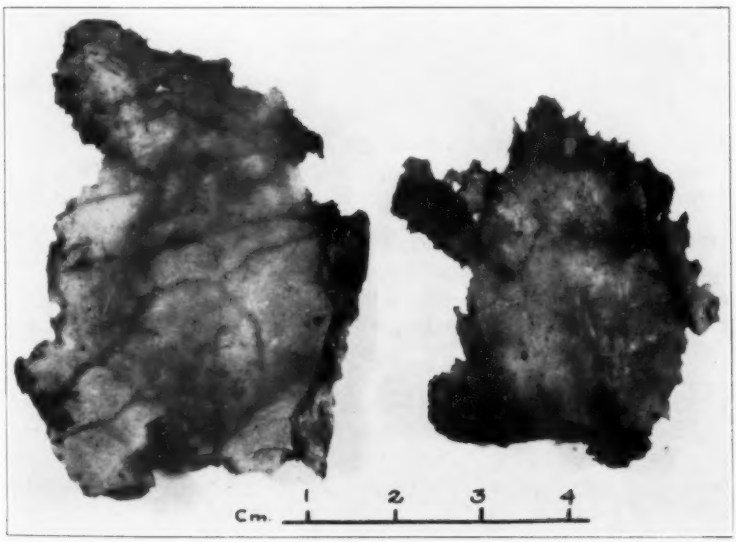

Fig. 3 (case 1).—Sequestrums, as in figure 2, showing the fairly intact inner table. The irregular margins of the fragment are well shown.

In either case, once the sequestrum has formed, the erosion of the margins begins, resulting in an irregular fragment. In instances of localized osteomyelitis this infectious necrosis may occur more or less en masse, owing to the original widespread process. Complete erosion of the bone may occur in circumscribed areas, resulting in holes in the sequestrum which may, by irregular erosion of the margin, become continuous with the margin, further adding to the irregularity of its shape. Why erosion should occur in such spots to this extent may be conjectured as being again due to the peculiarities of the local vascular channel arrangement. This irregular erosion and necrosis may result

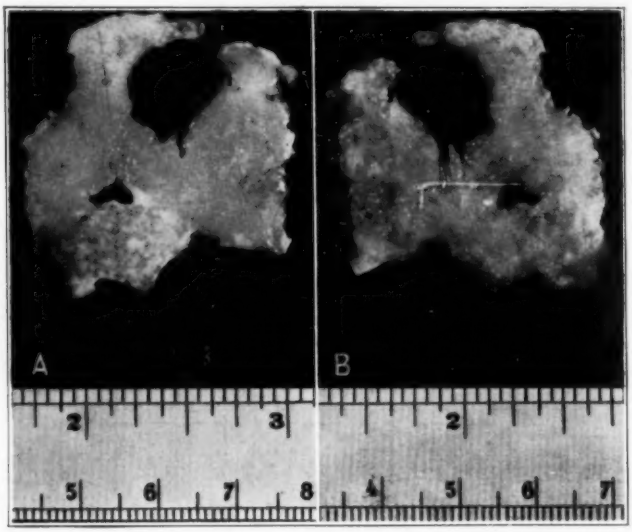

Fig. 4 (case 6).—Sequestrum, showing the outer (*A*) and inner (*B*) surfaces. The outer surface is comparatively smooth, showing little evidence of erosion from this surface. The inner surface shows marked erosion and perforation of both tables from this side.

in the separation of small flakes and fragments from the mother fragment, which may be discharged from the wound, or may undergo complete necrosis in situ.

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p. 49) states that the inner table is often more extensively destroyed than the outer one. This was the situation in case 6, in which an infectious necrosis took place in the larger fragments. In case 4, to the contrary, the outer table of the sequestrums was more extensively necrosed. This difference is probably to be explained largely on the basis of the blood supply. In fragments separated from the dura, necrosis occurs more readily in the inner table, owing to the facility of invasion along the vascular channels perforating the bone. When the dural attachment is retained, the outer table with its comparatively lesser blood supply is more apt to be necrosed.

PATHOLOGY

As has already been stated, it has been impossible to make a study of the pathologic process in our cases, owing to lack of radical surgical measures, and the fact that none of the patients died. It would undoubtedly be enlightening to know the details of the reaction taking place in the adjacent bone in the various types of lesions, which leads to ultimate healing. It will be necessary to refer to the work of McKenzie,[9] who studied the pathologic changes in spreading osteomyelitis of the skull secondary to frontal sinusitis. This type of osteomyelitis is similar to that following trauma. We are in accord with his observations, that the disease does not confine itself to the diploe, but may destroy the solid bone of the tables themselves. It is his opinion that the lesser the blood supply, the more apt the bone is to become infected. This likely accounts for the rapid necrosis of sequestrums when separated from their blood supply.

Laurens[10] found that thrombophlebitis of the diploic veins was found well in advance of the disease of the bone. It seems probable that, as the process is known to spread more actively toward the vault, there is a local thrombosis of the veins at the margin of the infection, with a retrograde extension of the thrombosis, owing to a backing up of the venous current. Infection spreading in this thrombus could easily account for the rapid spread of the disease. It also spreads by direct invasion of the diploic spaces and haversian canals by the infecting organism, a necessarily slower process.

The lesion itself is to be considered, according to McKenzie, as an infectious rarefying osteitis or panosteitis, leading to a more or less extensive destruction of all constituent elements. It may be divided into the following stages: (1) congestion, (2) pus formation in foci in the diploe, (3) diffuse involvement of the entire diploe and (4) penetration of the external and internal tables along vascular channels in the osseous tissue, with ultimate necrosis of the bone. In spreading osteomyelitis of the skull following trauma, there seems to be one essential difference from that secondary to frontal sinusitis. Rapid and direct invasion of the diploic veins takes place, with little lateral extension into the adjacent normal bone. The isolated sequestrum, however, shows evidence (case 4) of active invasion of the diploe and marked destruction of the outer table.

In the sclerosing and circumscribed types of traumatic osteomyelitis of the skull, a different picture is presented. In the localized types of osteomyelitis, even though there is no active or diffuse spread of the infection by way of the diploic vessels, engorgement of these vessels

9. McKenzie, Dan: Diffuse Osteomyelitis from Nasal Sinus Suppuration, J. Laryng. & Otol. **28**:6, 79 and 129, 1913.

10. Laurens, quoted by McKenzie.[9]

in the area surrounding the original focus is indicative of an abundant protective reaction. The central zone of inflammation and necrosis breaks down, often with the formation of a central sequestrum. Reaction in the surrounding bone soon develops, and the extent of the inflammation is limited to a variable degree by a sclerosing process. Proliferation of bone at the margin of the defect often reduces it in size. The final stage of the disease is represented by a defect in the skull with an eburnated, rounded margin.

In cases of a superimposed infection on a comminuted fracture of the skull, an interesting pathologic situation exists. Peculiarly enough, active invasion of diploic veins opening into the fracture lines outlining the defect is of rare occurrence. Furthermore, the margin of the bone shows little reaction in this form of sclerosis. The essential lesion is an infection-necrosis of the fragments within the area. If small, practically all of the fragments become readily involved. Some of the larger fragments, especially if at some distance from the point of infection, may escape (case 6). In the larger fragments that become involved, invasion of the diploic venous channels may occur along with erosion of the inner surface and the margins. These processes produce an irregular fragment, which is often broken into several parts before it is discharged.

As illustrated by our cases, it is evident that healing of the external sinuses may occur before all of the smaller sequestrums are discharged. Such fragments undergo necrosis and absorption in situ. Large fragments, however, act as foreign bodies—as sequestrums in other bones—and their presence delays final closure of the draining sinuses.

It must be admitted that other pathologic possibilities may, and likely do, occur. This discussion is necessarily based on the cases at hand, and, for lack of material on which histologic studies might have been made, there undoubtedly exist many gaps in the knowledge of the pathology of this lesion.

Intracranial Complications.—As characteristically seen in localized osteitis of the skull, extradural abscess is the most common intracranial complication. This accumulation of pus is the result of a downward spread of the infection through the inner table. Local dural hyperemia is followed by formation of granulation tissue and exudation of pus. In most instances an extradural abscess is evacuated spontaneously by dissolution of the overlying bone, but on occasion, as Pott himself learned, it is necessary to trephine and drain. This procedure is indicated when evidences of sepsis and localizing neurologic signs make their appearance in a recognized case of osteomyelitis.

In a recently studied case [8] an encapsulated and localized subdural, as well as an extradural, abscess was found and surgically drained. That this does not occur more frequently is in itself evidence of the

protective ability of the dura. Meningitis, sinus thrombosis and cortical and subcortical abscess of the brain are apparently rare complications, unless the infection is carried through the arachnoid and into the brain at the time of injury. It is easily possible for a septic meningitis to develop, should an extradural or particularly a subdural abscess remain undrained for any period of time.

REVIEW OF THE RECENT LITERATURE

There have been but few cases of traumatic osteomyelitis of the skull reported in the past few years. As has been stated, such instances have been sporadically cited in reports on injuries of the head, but case studies have been few in the recent literature. Howard Fleming [11] reported three cases following injury, in two of which the patients were operated on, and all recovered. Shea [12] reported a questionable case in which an injury preceded a frontal sinusitis, and osteomyelitis followed an operation on the frontal sinus. Dabney [13] also reported a case of osteomyelitis of the frontal bone following trauma, with recovery after repeated operations, on which occasions the diseased bone was rongeured away. A similar case was described by Zeno and Cames.[14] Stoian and Costescu [15] recently reported a case in which clinical cure was followed by jacksonian seizures, assumed to be due to some intracranial complication. Dr. Costescu told us that these manifestations were short lived and the patient was soon able to resume his military duties.

Such reports give only a meager insight as to the frequency of the condition, for it is likely that many such cases occur. It would be of interest to know what complications occur; what the mortality is after radical and conservative treatment, and what the duration of the various types of osteomyelitis might prove to be.

Viewed from a roentgenologic standpoint and the clinical course of the disease in the various cases, the following case reports, together with a roentgenographic history of each case, illustrate some of the essential points in the pathogenesis as well as the factors of treatment.

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11. Fleming, Howard: Osteomyelitis of the Skull, California & West. Med. **23**:985, 1925.

12. Shea, J. J.: Osteomyelitis of the Frontal Bone: Two Cured Cases, Ann. Otol., Rhin. & Laryng. **37**:500, 1924.

13. Dabney, V.: Osteomyelitis of the Frontal Bone: Report of Four Cases Presenting Problems in Etiology and Treatment, Arch. Otolaryng. **8**:177 (Aug.) 1928.

14. Zeno, L. O., and Cames, O.: Osteomielitis del frontal y absceso extradural con relatión de dos casas personales, Semana méd. **2**:915, 1928.

15. Stoian, C., and Costescu, P.: Osteomielita oaselor craniului si tratamentul ei actual, Rev. de chir., Bucuresti **34**:266 (July-Sept.) 1931.

REPORT OF CASES

CASE 1.—*Sclerosing osteitis of the occipital bone following local injury.*

History.—A musician, aged 22, was admitted to the hospital on March 4, 1929, with the complaint of tenderness and drainage from an "abscess" on the back of his head. He had struck the back of his head about three months previously while working under his car. Shortly afterward, he noticed a swelling with tenderness on the back of his head. This swelling ruptured spontaneously, and a small amount of pus was evacuated. A local physician enlarged the opening and removed a sequestrum, and then sent the patient to the hospital.

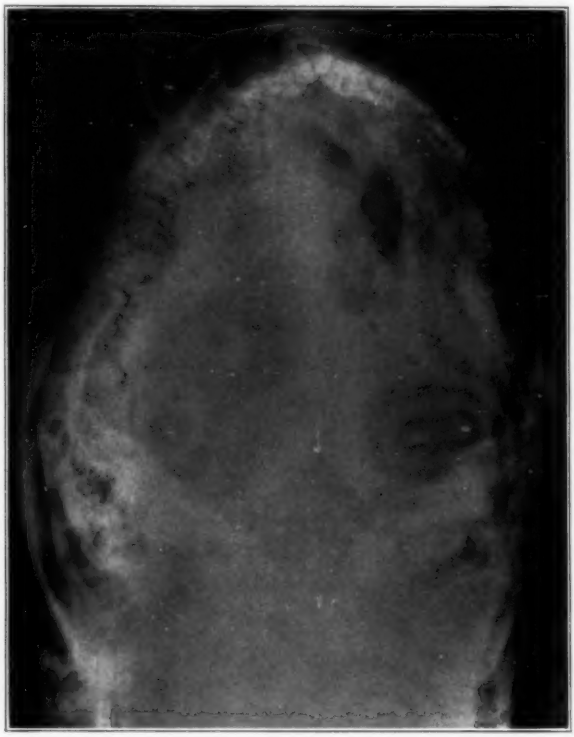

Fig. 5 (case 1).—Roentgenogram, showing sclerosing osteomyelitis in the left occipital region. The bridge between the lighter and darker areas finally sequestrated. It is likely that both tables were involved above, while the outer table alone was involved below.

Physical Examination.—The patient was a well developed and well nourished white man, presenting a draining sinus over the left occipital area about the size of a quarter. There were practically no signs of inflammation locally. The oral temperature was 99 F. Stereoscopic views of the skull revealed a small irregular area of destruction in the left occipital bone near the protuberance.

Course.—A conservative form of treatment was adopted, and the local wound began to close, with a decrease in the amount of drainage. A small sequestrum was removed on April 12. The patient was discharged from the hospital on

April 13, with instructions to return to the outpatient department for observation. He had regular dressings twice a week. Examination of the site of the wound four months later revealed a well healed scar with no drainage.

Course of Lesion Followed Roentgenologically.—At the time of admission, roentgenograms of the skull showed a small irregular area of destruction in the left occipital bone, which had involved both tables (fig. 5). The surrounding bone was thickened and sclerosed. No sequestrums were visualized at this time. On April 8, a second series of pictures revealed a small central sequestrum. As compared with the previous films, the margins of the involved area were smoother and the area was smaller, evidently due to some proliferation of bone in the region. The sequestrum referred to here was removed during the course of dressing the wound on April 12.

With steady improvement and cessation of drainage during the subsequent course of the condition, no further films were taken, and the patient was lost sight of after the wound had completely healed.

Comment.—This is the first example in the series of so-called "sclerosing osteomyelitis" of the skull following a local injury. It would no doubt correspond to "Pott's puffy tumor" of last century's surgical literature. In such cases the sequestrums formed are often discharged spontaneously through the draining wound, operative treatment, therefore, not being required other than the incision of the original swelling. This case ran a comparatively short course as compared with other cases in the series, about nine months in all.

CASE 2.—*Sclerosing osteitis of the skull following a blow on the head by falling timber. Long clinical course. Operative removal of central sequestrum and final healing.*

History.—A Mexican laborer, aged 67, was admitted to the hospital on March 18, 1929, with the complaint of local pain and tenderness and a draining wound in the right occipital region. About nine weeks previously he had been struck on the head by a falling timber while at work. This was followed after a week's interval by a large fluctuant swelling at the site of injury. The swelling had been opened by the family physician, and a large amount of pus evacuated. The wound showed no tendency to heal, and the patient finally appeared in the neurosurgical clinic.

Examination.—The patient was a well developed and well nourished Mexican, who presented a profusely draining sinus in the right occipital region with an external opening about the size of a dime. Foul, yellowish pus exuded from this opening. The temperature on admission was 101.6 F. Roentgenograms revealed an irregular localized area of decreased density in the right posterior parietal region with a marked thickening of the surrounding bone suggestive of sclerosing osteitis.

Course.—The customary conservative form of treatment was adopted, with daily dressings with balsam of Peru. Under this regimen, the drainage soon became less profuse, and there was a definite subjective relief of pain and discomfort. The patient was discharged from the hospital on May 17.

The patient was kept under observation for many months, during which the wound was dressed two or three times a week with alcohol or peroxide irrigations, and then treated with mercurochrome-220 soluble. On Oct. 22, 1930, because of the persistence of drainage, the patient was readmitted to the hospital, and the

Fig. 6 (case 2).—Roentgenogram, showing area of rarefaction in the right parietal region, possibly an extension of the original focus, seen here outlined on the occipital contour.

Fig. 7 (case 2).—Roentgenogram, showing sclerosing osteomyelitis of the right occipital region with formation of a central sequestrum.

wound carefully explored (by Dr. Adelstein). A small irregular sequestrum was detached from the margin of the involved area, and the wound incompletely closed, permitting of free drainage. Again daily dressings were made with balsam of Peru until there was but a small amount of drainage from the wound. The patient was discharged to the outpatient department on November 28. He was last seen in the clinic April 18, 1931, when the wound had closed.

Course of Lesion as Seen in Roentgenograms.—The first examinations were made on March 20, 1929, at the time of first admission, when an irregularity of density of the bone was observed in the right occipital region with some thickening of the vault about it. This bony reaction was therefore evident nine weeks after the original injury, and eight weeks after the first evidence of local infection.

A second series of pictures was taken on May 17, two months later, when the same general picture was presented, no sequestrum having formed in the interval. Two other small areas of rarefaction of the vault were found in the right parietal region (fig. 6), and in the line of the parieto-occipital suture. The nature of these rarefied areas was never definitely settled, but the possibility of a regional metastasis of the infection was thought of. These areas did not change during the course of observation, and were present at the time of final discharge. Reexamination on July 30 revealed no change in the condition.

On April 11, 1930, the area of involvement of the bone had become slightly larger, and was then about 5 cm. in diameter. Within this area of moth-eaten appearance, there were some small denser shadows, suggesting that a sequestrum might be forming (fig. 7). There also seemed to be some enlargement of the diploic spaces above and anterior to the area, as though some invasion of these spaces had taken place. On July 9 and October 23, anteroposterior views revealed the slow development of a well outlined sequestrum attached to the surrounding solid bony margin by a narrow pedicle above and below.

The final pictures of the series were taken on Feb. 2, 1931, and revealed the area to be decreased in size with definite sclerosis of the surrounding bone. Some proliferation of the surrounding bone had taken place.

Comment.—This patient had the typical sclerosing type of osteomyelitis of the skull following injury, characterized by a long clinical course and final healing, with sclerosis of the bony margin of the defect. There was some tendency toward filling of this defect by proliferation of the bony margin. Invasion of the diploic spaces was suggested in the roentgenograms on one occasion, which remained localized, due probably to the protective reaction in the bone which developed coincidently with the infectious process. The only recourse to surgical intervention was indicated by the formation of a well outlined sequestrum.

CASE 3.—*Circumscribed osteomyelitis of the skull following partial avulsion of the scalp with destruction of a portion of the outer table.*

History.—A mechanical engineer, aged 52, was struck by an automobile while walking down the road. He suffered multiple abrasions and lacerations about the head and face, as well as a partial avulsion of the scalp over the right posteroparietal region. This occurred during the latter part of December, 1929. He was treated by a local physician until his removal to Los Angeles, the details of the treatment not being known. At the time of his admission to the hospital on Jan. 27, 1930, there were considerable local pain and a profuse drainage from the wound, which was opened widely.

Examination.—The patient was a well nourished and well developed white man of middle age, whose general condition seemed to be good; his temperature was normal. A large jagged laceration of the scalp was found in the right posteroparietal region, exposing an area of skull 6 by 8 cm. There was a profuse purulent discharge from the edge of the wound, and the bone itself appeared dark in color. It had a ragged appearance, owing to the irregularities in the exposed diploe, from which pus oozed at numerous points. Stereoscopic views of the skull at this time revealed a circular area of mottling of the bone, 4.5 cm. in diameter, which was diagnosed by the roentgenologist as osteomyelitis of the skull.

Course.—The laceration and the exposed area of the scalp were treated conservatively by daily dressings with balsam of Peru. The subjective symptoms of headache and vertigo (probably posttraumatic in the latter instance at least) soon disappeared, granulations began to fill in the exposed area, and drainage became much less. The patient left the hospital against advice on April 4, going to the

Fig. 8 (case 3).—Local osteomyelitis of the skull following traumatic abrasion of the outer table. The mottled appearance of the area is characteristic.

Veterans' Hospital in Sawtelle, Calif. He remained under treatment in that institution for about a year, where the same sort of treatment with balsam of Peru was carried out. During this interval he was seen twice in our outpatient clinic, on Dec. 6, 1930, and on March 27, 1931, at which times roentgenograms of the skull were taken. At the time of his last visit, the wound had completely closed.

Course of the Lesion Followed Roentgenologically.—The series of x-ray films were taken at the time of the patient's admission on Jan. 27, 1930, and revealed the typical mottled area in the right parietal region characteristic of osteomyelitis of the skull (fig. 8). No sequestrum was demonstrated at this time. The patient left the hospital rather suddenly against advice, and no further pictures were taken at this time. On Dec. 6, 1930, he returned to the clinic, and roentgenograms showed a narrowing of the original area, although its central portion appeared clear, as though a sequestrum had formed and had been discharged or surgically removed. Below and posterior to the original area was another area of equal size, showing a diffuse mottling suggestive of an extension of the infection into

the diploe of this region. The area was irregular in outline, and was limited by the parieto-occipital and the temporoparietal sutures. The reduction in size of the original area appeared to be due to a proliferation of bone from the inner table of the skull. Its margins were rounded, and its increased density suggested an early sclerosis.

At the time of the patient's last visit to the clinic on March 27, 1931, at which time the wound had closed, a right lateral stereoroentgenogram of the skull revealed a progressive narrowing of the original area of osteomyelitis. This was again found to be due largely to the proliferation of bone of the inner table, the defect in the outer table remaining about its original size. The defect in the inner table was 3.5 by 2 cm. in its greatest transverse diameters. The bone about the defect had become thickened and sclerosed. The mottled area previously described below the original area was less conspicuous, healing evidently having been going on.

Comment.—This instance of osteomyelitis of the skull was due to a direct implantation of contaminated material into the exposed diploe of the skull. At the time of admission, almost a month after the accident, the diploic spaces were grossly infected. A more complete follow-up was impossible, owing to the lack of cooperation on the part of the patient, but fortunately he fell into the hands of physicians who gave him the same type of treatment, it having been recommended on his departure. It seems evident that invasion of adjacent diploic spaces may occur to some degree from such a lesion.

CASE 4.—*Spreading osteomyelitis of the vault developing in the margin of an operative defect.*

History.—A white man, aged 36, a painter, was injured when the automobile he was driving was struck by an electric interurban train on the afternoon of March 11, 1928. A wound of the scalp was sutured by the physician rendering first aid. The patient was forwarded to this hospital, where he arrived several hours after the accident.

Physical Examination.—The patient was conscious but rather confused, and there was profuse bleeding from the right ear. A wound 3.5 cm. in length was found in the right parietal area, which had been closed without drainage. The pupils were equal and reacted to light. All reflexes were present and equal on both sides. Lumbar puncture revealed the spinal fluid to be uniformly bloody, and under slightly increased pressure. Flat plates of the skull revealed what appeared to be a linear fracture in the right parietal region, extending downward into the base anterior to the mastoid portion of the temporal bone.

Course.—The patient did fairly well for the following four days, and then a left hemiparesis developed, with clouding of consciousness and an elevation in temperature to 103 F. The deep reflexes on the weakened side were increased over the right, but no Babinski sign or ankle clonus was demonstrated. A right subtemporal decompression was performed twelve days after admission by Dr. George H. Patterson, and a large extradural clot was evacuated. The patient's condition began to improve immediately after the operation. This improvement was short lived, however, for three days later there was a rise in temperature, and swellings of the right elbow, left knee and right sternoclavicular joints made their appearance. It was also noted that the original laceration in the right parietal area was draining a moderate amount of foul-smelling pus. The wound in the scalp was

opened and drainage instituted. The abscesses in the regions of the involved joints were also opened, and culture of the pus showed Streptococcus viridans. The patient's condition again began to improve, in spite of profuse drainage from the incised abscesses and the original wound in the scalp.

The decompression wound in the right temporal region soon became infected secondarily to the original wound in the scalp. This wound broke down completely and drained a yellowish pus in profusion. Because of the persistent drainage from the operative site, osteomyelitis of the underlying skull was suspected, and roentgenograms were taken on May 14, 1928. The films showed a diffuse destruction of bone at the margin of the decompression defect and a marked prominence of the diploic channels posterior to it. The wound was treated conservatively with daily, or even more frequent, dressings with balsam of Peru, which resulted in

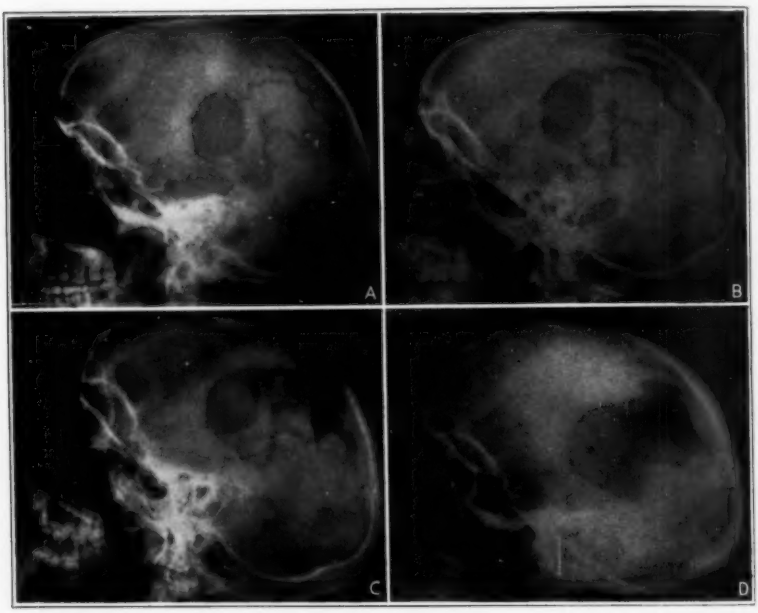

Fig. 9 (case 4).—*A*, roentgenogram, showing original oblique fracture line, the operative defect and evidence of osteomyelitis following diploic venous channels and mottling of the bone. *B*, roentgenogram, showing advancing osteomyelitis which is separating a large irregular sequestrum. Smaller sequestrums are formed by the breaking off of the "horns" of the larger fragment. *C*, roentgenogram, showing the large sequestrum entirely separated, with increasing erosion of its margin. Smaller sequestrums are forming by the breaking off of its margins. *D*, roentgenogram, showing the irregular defect in the skull left by the removal of sequestrums. There appears to be some proliferation of bone from the inner table in the upper margins of the defect, evidently an attempt to obliterate it.

but little change in the character and amount of drainage. Because of this condition, the patient was kept under observation in the hospital for about a year, when further roentgenograms of the skull were taken (April 15, 1929), which revealed the formation of a large irregular sequestrum above and posterior to the

decompression defect. This was removed surgically by Dr. George H. Patterson on April 24, 1929 (figs. 2 and 3).

The wound continued to drain profusely for several months, but finally began to fill in with granulation tissue, with lessening of the amount of pus. During this interval the wound was dressed daily with balsam of Peru. The patient was discharged to the Veterans' Hospital at Sawtelle, Calif., on Jan. 4, 1930. A letter from that institution dated April 15, 1930, stated that the wound in the skull was still draining. A more recent communication states that the wound healed after the defect in the skull had been closed by grafts by Dr. Eliott Alden.

Course of the Disease Followed Roentgenologically.—The first films were taken on March 12, 1928, immediately after the injury, and revealed a linear fracture extending through the right parietal and temporal bones into the base. The first evidence of osteomyelitis was shown on May 14, 1928, when a right lateral stereoroentgenogram of the skull revealed an extensive and diffuse mottling of the bones of the skull in the right parietal region, marked by definitely enlarged diploic channels extending upward and posteriorly from the decompression defect (fig. 9*A*). On May 28, 1929, a similar picture was presented, except for the appearance of an irregularly oval area posterior to the operative defect, and connected to the inferior diploic channel. Films taken on Aug. 29, 1928 (fig. 9*B*), showed essentially the same findings, except for a definite widening of the diploic channels and an increase in the haziness of the bone in the region. Films taken on Dec. 20, 1928, and Feb. 23, 1929, revealed a progressive widening of the diploic channels outlining the sequestrum, with an increasing irregularity of its margins. On April 15, 1929, the sequestrum was found to have separated itself entirely from the surrounding bone, and several smaller fragments had been separated from the larger mass (fig. 9*C*). There was a large clear area in the upper part of the involved area, as though a considerable portion of the sequestrum had undergone complete destruction. The large sequestrum and several smaller fragments were removed at operation on April 24, 1929. Subsequent right lateral stereoroentgenograms of the skull, taken on June 17, Oct. 1 and Nov. 22, 1929, revealed a progressive rounding off of the margins of the defect, with occlusion of the regional diploic channels, a lessening of the moth-eaten appearance of the skull and an increasing density of the bone forming the margin of the defect (fig. 9*D*).

Comment.—This is an excellent example of the spreading type of traumatic osteomyelitis of the cranial vault. In this instance, a direct invasion of the diploic channels was possible in the margin of the operative defect in the bone, an unfortunate necessity owing to the occurrence of an interval hemorrhage. The history is that of a slowly developing sequestrum, outlined by converging diploic channels with final separation of the fragment by erosion through the inner and outer tables bounding these channels. Surface interference was limited to simple enlargement of the draining sinuses and removal of sequestrums without interference with the adjacent bony margins in which the battle was still being waged—quite successfully, as time showed. The interval treatment was conservative, with daily dressings with balsam of Peru. Of interest in this case are the metastatic foci elsewhere in the body. McKenzie [9] stated that such foci are not uncommon following traumatic osteomyelitis of the skull, but they are rare following osteomyelitis secondary to suppuration of the frontal sinus.

CASE 5.—*Osteomyelitis of bone fragments secondary to compound comminuted fracture with infection in overlying wounds of the scalp.*

History.—A white man, aged 43, a restaurant proprietor, was attacked while closing his place of business on the night of Feb. 7, 1930. He was picked up shortly afterward by the police, and was taken to the receiving hospital, where his scalp wounds were treated and closed with skin clips without drainage. He was transferred to this hospital at 2:00 a. m. on February 8, conscious and rational, but complaining of much pain in the region of the wounds in the scalp.

Examination.—There was an enormous hematoma over the right parietal and occipital areas, with four jagged lacerations in this region. There was, in addition,

Fig. 10 (case 5).—Osteomyelitis of fragments of bone following comminuted fracture in the right occipital region. Discharge of some of the fragments through the open sinus has taken place. Healing is indicated by a rounding off of the irregular contour of the defect.

a bilateral orbital ecchymosis, the left eye being swollen shut. The patient appeared to be in good general condition, and there was no evidence of any intracranial complication. Stereoscopic views of the skull revealed an extensive comminuted and slightly depressed fracture of the skull in the right occipital region, with radiating fracture lines extending into the base.

Course.—Because of the depression of the fragments, an operation was performed under local anesthesia by Dr. George H. Patterson, and the depressed fragments were elevated. The wound healed readily, and at the time of the patient's discharge from the hospital on February 24, there was only a small

amount of serous drainage from one end of one of the wounds. He was instructed to return to the outpatient clinic for further dressings.

The patient failed to return for dressings as instructed, and on April 25, 1930, presented himself at the receiving hospital because the wound had broken down and continued to drain, possibly due to a lack of proper dressing and attention. He was again referred here, and the wound was dressed twice a week in the outpatient department. On May 5, a small sequestrum was removed by the physician in charge, and the patient was again sent to the neurosurgical clinic, where examination and x-ray pictures of the skull confirmed the suspicion that osteomyelitis had developed.

The patient was readmitted to the hospital on May 21, with profuse drainage from the old operative site. A small sequestrum was removed from the wound on May 23. The wound was dressed daily with balsam of Peru, and while the amount of drainage decreased considerably, it was consistently present. Another small piece of bone was removed on September 2. He was discharged on September 30, at which time the wound was entirely healed. He was seen several months later, at which time the wound was well healed, there having been no drainage during the interval.

Course of the Lesion Followed Roentgenologically.—The first evidence of infection in the fragments was observed in the series of pictures taken three months after injury, at which time the fragments had decreased in size and appeared thinned and irregular. There was some rounding off of the marginal bone, with little tendency to sclerosis (fig. 10). There was no extension of the infectious process into the surrounding bones. Two and a half months later, additional roentgenograms were taken, when the fragments were found to have decreased in size and number, evidently due to necrosis and discharge of some of the fragments. The margins of the defect had rounded off to a still greater extent, and an additional degree of sclerosis had taken place.

Unfortunately, further pictures were not taken at the time of the patient's release from the hospital. The wound had completely healed, but additional fragments must have remained. The fate of such fragments would be of interest, whether they undergo complete necrosis, or whether they may serve as points for bony proliferation when the infectious process has run its course.

Comment.—This is the first of two cases of osteomyelitis developing in the fragments of a comminuted fracture of the skull. The process is quite characteristic, with draining sinuses, necrosis and discharge, as well as sequestrums of the bony fragments and rounding off and moderate sclerosis of the surrounding bony margin. The following case is of even more interest in this regard.

CASE 6.—*Osteomyelitis of bone fragments following late infection of an operative wound for elevation of comminuted depressed fracture.*

History.—A boy, aged 4 years, was admitted to the neurosurgical service of the hospital on July 30, 1931. He had fallen from his father's automobile while the vehicle was in motion, striking his head on the pavement; he was rendered unconscious for about ten minutes. He was conscious and rational at the time of admission.

Examination.—The boy appeared to be in good physical condition; the temperature was 100.0 F., and the pulse rate, 108. There were several superficial brush burns of the scalp on the left side of the head and a large hematoma in the left

parietal region. Roentgenograms of the skull revealed a markedly comminuted fracture of the left posteroparietal region of the vault, with depression of several fragments.

Course.—On Aug. 1, 1931, the depressed fragments were elevated and replaced through a semilunar incision (by Dr. Courville), following which the wound healed by first intention. Acute tonsillitis and a pustular infection of the skin of the trunk and of the scalp developed on the fifteenth postoperative day. Two of the scalp foci developed within the region of the operative site, one immediately adjacent to the incision and the second in the midportion of the scalp. The skin incision became infected, broke down and discharged in its lower portion adjacent to one of the local pustules. A second focus developed into an abscess about the size of a half dollar within the tissues of the galea. Smear and culture showed the infecting organism to be Staphylococcus aureus. The location of the draining sinus in the wound, with the amount and persistency of the discharge, gave rise to the suspicion that the infection had gained access to the subaponeurotic space with infection of the bone itself. This was verified by roentgenograms of the skull, which showed the bony margins of one of the large fragments to be hazy and irregular.

The bone was reexposed (by Dr. Courville) through the original incision, and granulation tissue was found extending down to the skull itself. The abscess in the scalp had broken through the galea, and pus was present over the bone, although not in any great quantity. The bone of the major fragments appeared to be normal grossly and union with the surrounding bone had already begun, so it was hoped that the fragments would not be sacrificed. The wound was loosely closed, with drainage in the incision and in the abscess of the scalp. Following the operation there was extensive drainage from all openings. The wound was dressed daily with balsam of Peru. On September 14, a small triangular sequestrum was recovered from one of the sinuses.

Nothing noteworthy occurred in the course of recovery until on Jan. 15, 1932, pain developed in the left ear, followed by rupture of the drum and a purulent drainage. Smear and culture revealed the infecting organism again to be Staphylococcus aureus. The physical condition remained good; there were no unusual elevations in temperature, and the child was able to be up and about the ward. On January 22, an irregular margin of a large sequestrum presented itself at the opening of one of the draining sinuses, and this was removed two days later with little difficulty.

It was thought advisable to give the patient Staphylococcus aureus bacteriophage in an attempt to accelerate healing of the wound. This was given in amounts of from 0.25 to 1 cc. daily. The wound closed rapidly, possibly due to the action of the bacteriophage, but likely also facilitated by the removal of the bony sequestrum. The child was discharged from the service on March 26, with a dry scab over the last of the sinuses, and repeated observations since that time have revealed no tendency toward a recurrence of the infection.

Course of the Lesion Followed Roentgenologically.—The first evidence of infection in the skull was found on Aug. 24, 1931 (fig. 11 *A*), less than four weeks after the injury, and about a week after infection, at which time there was a haziness of the margins of the fragment in the lower portion of the depressed area, with a decrease in density, suggesting osteomyelitis. A small sequestrum was recovered on September 14, probably one of the smaller fragments of the original injury. Left lateral stereograms of the skull, taken on October 24, showed a marked irregularity of the lower fragment with haziness of its substance and an erosion of its midportion. The lower portion of this fragment had become sepa-

rated, so that two small sequestrums were seen in the films. The large sequestrum was still in place at this time. Another series of films taken on Jan. 23, 1932, revealed a forward and downward displacement of the large lower fragment, which was now irregular in contour and presented a large defect in its midportion (fig. 11 *B*). It was one corner of this fragment that presented in one of the sinuses, and which was removed in toto the day following the taking of the roentgenograms. The final pictures were taken on March 23 (fig. 11 *C*), which showed a rounding off of the contour of the bony defect. There were faint shadows in the area, which might have been small sequestrums. It was of interest to note that the upper fragment remained unaffected by the infectious process, and that bony union with the surrounding skull had already begun.

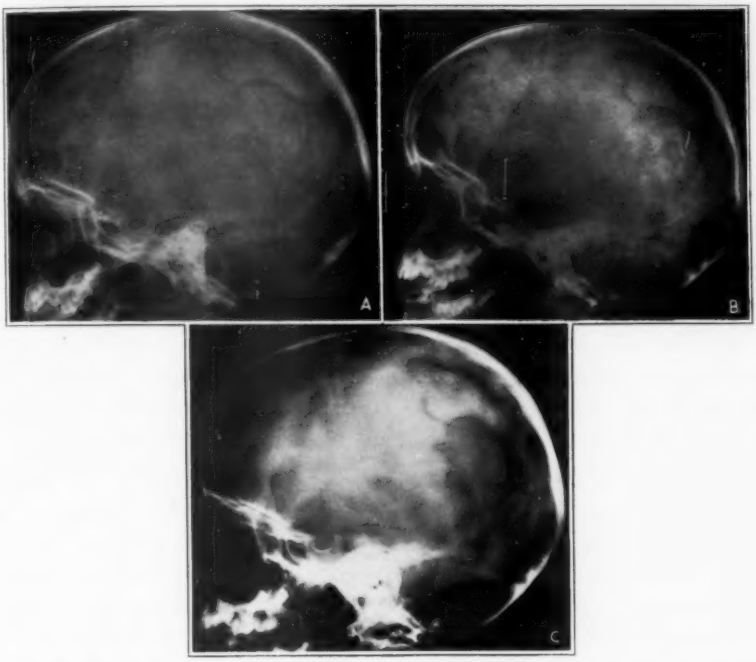

Fig. 11 (case 6).—*A*, osteomyelitis of fragments of bone following comminuted fracture in the left parieto-occipital region. First evidence of infection in the bone, less than four weeks following injury. Invasion of diploic veins of the lower fragment is indicated by irregular lines within its margins. *B*, extensive erosion, fragmentation and dislocation of the original sequestrum. *C*, defect in the skull left by the removal of a large sequestrum. Faint shadows within the outline of the defect suggest that smaller sequestrums may still be present.

Comment.—This case is unusual in that an incidental infection of the scalp in a small patient evidently susceptible to staphylococcic infections was responsible for a rather complicated history of what otherwise might have been a simple case. The condition is probably to be especially classified with case 5, as a modified osteomyelitis of the skull, in

the sense that the process spread in one of the large fragments in a rather typical way. The process did not extend in the surrounding healthy skull, and, peculiarly enough, not in the upper fragment, somewhat more remote from the original infection. With the probability in mind that there was a systemic low threshold of resistance to the staphylococcus, a course of treatment with bacteriophage was instituted. This appeared to hasten the healing process, and it is probably wise in selected chronic cases to use this means in the treatment of the condition.

TREATMENT

The question of radical versus conservative treatment of osteomyelitis of the skull has provoked much discussion and at this time there appears to be a tendency in some clinics to handle such cases in much the same manner as osteomyelitis of the long bones of the body, that is, by early radical surgical intervention. As indicated by a study of the peculiar nature of the bones of the skull, their blood supply and the drainage system and with due appreciation of the opportunity for infection to spread with ease and rapidity through the diploe and enclosed system of veins, it is our opinion that radical surgical intervention has but little place in the treatment of traumatic osteomyelitis of the skull. This is in contradistinction to the principles of treatment of acute osteomyelitis elsewhere in the body, and it is felt that the good results in this series are in no little measure due to the confining of treatment to more or less conservative measures.

Preventive Care.—The prevention of osteomyelitis of the skull is naturally of prime importance and concerns itself mainly with the careful handling and thorough débridement of the wounds in cases of injury to the head presenting compound fractures with indriven fragments of bone and débris from the street. It is necessary to remove all fragments of comminuted bone, hair and other extraneous materials, which always mean potential infection in these cases. A thorough débridement of irregular margins of wounds after the removal of all foreign material will often allow healing per primum. It has also been our practice thoroughly and repeatedly to iodinize all wounds extending through the galea in the course of exploration for underlying fractures.

Plan of Treatment.—When first seen, the active case may present an infected appearing wound of the scalp with irregular edges and draining variable amounts of foul-smelling pus. A roentgen examination at this time will show the type of involvement of the bone present, although it may be anticipated by the history of the case. The local treatment consists of daily dressings with careful cleansing of the wound

and application of balsam of Peru,[16] which in our experience has found a definite place in the therapy of this condition. This substance is slightly antiseptic, keeps the wound moist and favors the formation of healthy granulation tissue. Exuberant granulations that threaten to close draining sinuses should be cauterized with a silver nitrate stick.

The process of sequestration is often slow, and should be checked roentgenologically every three to four weeks. The time of separation of the infected fragments depends on the virulence of the infection and the type of lesion. In some cases the sequestrum is spontaneously discharged, and is found at the time of the daily dressing. If the sequestrum is large, it may be necessary to take the patient to the operating room for its removal. It is necessary to enlarge only the opening of the discharging sinus in order to permit the passage of the bony fragments.

Healing does not take place, as a rule, until all large sequestrums have been discharged or removed. In both of our cases of osteomyelitis of fragments in comminuted fractures healing has occurred with small fragments still being present. It may be justifiable on occasion to remove well formed sequestrums surgically in an attempt to shorten the course of the infection.

At no time, in our opinion, is it warranted or necessary to smooth the surrounding edges of the defect in the skull, as it can be readily seen that this procedure only tends to open widely the diploic spaces and to permit the spread of the infection. In other words, the most rational type of surgical treatment to be employed for traumatic osteo-

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16. The use of balsam of Peru for infections about the head is not a new departure in the field of therapeutics. In 1665, Peter de Marchettis (Med. Chir. **7**:11, 1665; quoted by Ballance, C.: A Glimpse Into the History of Surgery of the Brain, New York, The Macmillan Company, 1922, p. 88), reported a case of what seemed to be an extradural and subdural abscess which was treated with this substance after trephining. His description of the case is interesting:

"I remember having a consultation with the famous D. Julio Sala, professor at Pavia, about a man who had been wounded in the head with a dagger. Not only was the bone injured, but the membranes and even the brain. The external wound has been treated by certain practitioners and a cicatrix had formed. After two or three months the patient was troubled with epilepsy and had a fit twice or three times a month. When asked by Professor Sala whether he had ever had an injury to the head, he replied that he had, and pointed out the place. I immediately inserted a probe beneath the crust, and found a penetrating wound, and proceeded at once to operation, and the opening of the parts. The next day I applied the trephine; yellow pus escaped. For 20 days I applied over the brain black western balsam, with the use of which the wound granulated, and in the 30 days the patient was cured of his wound and of his epilepsy."

It is possible that balsam of Peru has been used by others in the treatment of osteomyelitis of the skull, but such reports have not made their appearance in the literature to our knowledge.

myelitis of the skull, under ordinary circumstances, is simple removal of completely detached sequestrums. The occurrence of an extradural abscess that does not drain, or the formation of a secondary subdural abscess, necessitates exploration and drainage, preferably at the site of the original bony necrosis. It may be necessary judiciously to enlarge the opening made by the burr, for an extradural abscess may not be located immediately beneath the area of focal necrosis.

Constitutional Measures.—It is of importance to build up and maintain the resistance of the patient, who usually faces a long clinical course of months with this type of infectious lesion. We have employed the use of such measures as exposure of the body to ultraviolet light or the sun, and the administration of cod liver oil in run-down patients or in the case of children. It is best that such patients be ambulatory, and be permitted outdoors as much as possible. Provided no complications arise, these patients may be treated in the office and, with suitable protection, may carry on their occupations.

Our experience with specific bacteriophage in this condition has been limited to but one case, and no definite opinion can be offered as to its value. In this case (case 6) it seemed rapidly to shorten the course of the infection, although the removal of a remaining large sequestrum also undoubtedly influenced healing to a great extent. This measure should be instituted in well selected cases, for it probably has its place here as in the treatment of other chronic pyogenic infections.

SUMMARY AND CONCLUSIONS

1. Traumatic osteomyelitis of the flat bones of the skull is a somewhat uncommon complication of injuries of the head, judging from the reports in the literature and our own experience. It may be of more frequent occurrence, however, than available information would lead one to believe. It is preventable in many cases by suitable treatment of the original wounds of the scalp.

2. A brief review of the anatomic factors that determine the course of the disease is given. The diploic spaces between the tables, together with the enclosed venous system, favor dissemination of the infection, although early local reaction usually prevents this from taking place.

3. A suggestive classification of the lesion is based on the pathologic changes and the roentgenographic appearance of the lesion: (1) localized osteomyelitis, (2) spreading osteomyelitis and (3) infectious necrosis of fragments in comminuted fracture of the skull. Cases of localized osteomyelitis may be subdivided into (*a*) sclerosing osteitis following local injury with an opened or intact scalp and (*b*) circumscribed osteomyelitis in which infection is implanted directly into the

diploe after abrasion of the outer table of the skull. The type of lesion may be anticipated by recognition of the mode and time of entrance of the infecting organism.

4. The mode of invasion and spread of the infection, together with the probable pathologic change in each type of osteomyelitis, is considered. The pathogenesis of the formation of sequestrums is also discussed.

5. A series of six cases illustrating the various clinical types of the disease is presented. The course of the disease is followed roentgenologically in each case.

6. The plan of treatment has been essentially conservative, consisting of daily dressings with balsam of Peru. This substance favors the subsidence of infection and the development of granulation tissue. It is necessary to keep draining sinuses open by controlling the growth of granulations, a silver nitrate stick being used when necessary. Surgical intervention is limited to the removal of sequestrums that cannot be discharged through draining sinuses.

SNAPPING SCAPULA AND HUMERUS VARUS

REPORT OF SIX CASES

HENRY MILCH, M.D.
AND
M. S. BURMAN, M.D.
NEW YORK

The presence of friction sounds in the region of the scapula has not gone unnoticed either by the internist or by the surgeon. The daily practice of auscultation of the chest has necessarily led to the discovery and differential diagnosis of sounds extraneous to the pulmonary tissue which might lead to erroneous conclusions. In the literature of the Continent a few articles devoted to a consideration of this subject have appeared in the German, Italian and French languages. In English, however, hardly anything concerning it has come to our knowledge, and we make this our excuse for presenting a brief review of the subject.

Credit for the recognition of this condition must be given to Boinet,[1] who was not able to determine the exact causation of the sound. Some time later Galvagni [2] had the opportunity of observing several phthsical patients in whom scapular sounds were present. He was of the opinion that these sounds occurred in such patients as a result of their general emaciation, and the possible development of a bursa between the muscles of the scapula and the wall of the chest. However, subsequent observations by other authors have demonstrated that scapular grating or snapping may be found in a number of different pathologic conditions, as well as in relatively normal persons presenting no subjective symptoms whatsoever. Indeed, Lotheissen,[3] who interested himself in the mechanism of the production of these sounds and who, by practice, was able to develop them in himself, naively remarked that "with time, one acquires a certain virtuosity in producing noises."

Scapular grating or snapping, the expression of some anomalous condition between the ribs and the undersurface of the scapula, is a tactile-acoustic phenomenon, which has been observed in varying intensity in different persons. In some, there may be a loud snap, clearly audible at a distance of several feet, while in others the noise

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From the service of Dr. H. Finkelstein, at the Hospital for Joint Diseases.

1. Boinet: Bull. Soc. de chir. **8**:458, 1867; quoted by Küttner, H.: Deutsche med. Wchnschr. **30**:534 and 580, 1904.

2. Galvagni, E.: Med. Jahrb., 1873, p. 274.

3. Lotheissen: Med. Klin. **4**:51, 1908.

may be reduced to a fine grating sound, barely perceptible to the touch. The intensity of the sound can in no wise be considered as an indication either of the severity of the pathologic condition or of the degree of disability occasioned by its underlying etiologic factors. Mauclaire [4] divided the noises into three main classes: *froissement,* a gentle friction sound, which he considered entirely physiologic in nature; *frottement,* a sound of somewhat louder character, and *craquement,* a loud snapping noise, invariably of pathologic import.

The frequency with which the physiologic friction sounds have been observed appears to vary within a wide range. Bassompierre,[5] in a study of 72 men, noted scapular crepitus as a gentle rustling sound in 51. This crepitus was noted over either the superior or the inferior angle of the scapula and over either half of the body, and apparently bore no relation to age or occupation. Grünfeld [6] found scapular crepitus in 31 of 100 normal people whom he studied. De Laroquette [7] observed scapular crepitus in 8.2 per cent of 620 normal persons. This type of physiologic scapular noise would be of no more than academic interest were it not for the fact that it may be heard quite frequently in tuberculous patients, according to the experience of Kirmisson.[5] From this point of view, the importance of recognizing and differentiating these purely physiologic from pathologic intrapleural sounds is apparent and need detain us no longer than to call attention to their existence.

Our main interest may perhaps better be devoted to the latter two categories described by Mauclaire. A fairly careful review of the literature reveals that cases in which the scapular noise becomes abnormally loud are relatively quite rare. In 18,000 persons, Lotheissen found only 1 case in which the scapular noise could be considered loud, and no case at all in 7,000 patients confined to bed and 40,000 ambulatory patients in which true snapping of the scapula was observed. Similarly, Betke,[8] who had a large military experience, found not a single case of snapping scapula. Nevertheless, a sufficient number of cases have been reported so that some classification has been possible. From a study of these cases, in which either unusually loud scapular noises or snapping was found, it appears that the causes of these sounds may be divided into three main groups:

(*A*) Those due to changes in the bony structure of the undersurface of the scapula, or of the wall of the chest.

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4. Mauclaire: Bull. et mém. Soc. d. chirurgiens de Paris **30**:164, 1904; Gaz. d. hôp. **78**:351, 1905.

5. Quoted by Küttner, H.: Deutsche med. Wchnschr. **30**:534 and 580, 1904.

6. Grünfeld, G.: Arch. f. orthop. u. Unfall-Chir. **24**:610, 1926.

7. de Laroquette, M., quoted by Whitman, Royal: A Treatise on Orthopædic Surgery, ed. 9, Philadelphia, Lea & Febiger, 1930, p. 248.

8. Betke: Beitr. z. klin. Chir. **82**:31, 1913.

(*B*) Those due to changes in the musculature intervening between the scapula and the wall of the chest.

(*C*) Those due to changes in bursae normally or abnormally present between the scapula and the wall of the chest.

To these may be added two other groups, which are incapable of proper classification because of a lack of exact knowledge either of the mechanism of production or of the underlying pathology.

In the former of these two groups are several cases in which no reason could be assigned for the production of scapular snapping. Axmann [9] described the case of a girl of 18 who attributed the development of the sound to the carrying of books. X-ray pictures were negative. No treatment was given, because there were no functional disturbances. Betke reported the case of a fusileer, in whom the sound heard at the superior angle of the scapula appeared following musket exercises. Conservative treatment was of no avail, and the patient was finally discharged with a 20 per cent disability. A second case seen by Betke occurred in a man 24 years old, in whom the sound was noticed following the lifting of a weight. At operation nothing, save some possible thinning of the subscapularis fibers, was noted. A four-cornered flap of the trapezius muscle (operation of Mauclaire) was placed between the anterior serratus muscle and the ribs. Both pains and snapping disappeared following operation.

In the latter of these groups is to be placed a not inconsiderable number of cases which appear to be associated with certain occupational activities, such as dressmaking, needle working, piano playing and baking. Whether the noise is to be accounted for by reason of excessive use of the scapular muscles or whether it is to be explained solely on the basis of atrophy of the subscapularis muscle alone cannot be positively determined. Jacoby [10] reported 5 cases appearing in sportsmen. Terrillon [11] reported several cases of this nature. In 1, a baker 20 years old, snapping had been present for about two years. A brace which Terrillon applied for the immobilization of both scapulae restored the patient to full functional capacity. The second case was that of a man, who found it necessary repeatedly to raise his arm forcibly above his head. Snapping, audible at a distance, had been present for from three to four months, and had persisted, despite a change of occupation. Zaphiriadès [12] examined a seamstress, aged 17, with unexplained scapular crepitus and a feeling of oppression between the shoulder blades.

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9. Axmann: Deutsche med. Wchnschr. **30**:955, 1904.

10. Jacoby, P.: Ugesk. f. læger **84**:1071, 1922.

11. Terrillon: Arch. gén. de méd. **24**:385, 1874; Bull. et mém. Soc. de chirurgiens de Paris **2**:725, 1876; Bull. gén. de thérap. **46**:8, 1879.

12. Zaphiriadès, A.: Contribution à l'étude du frottement sous-scapulaire, Thèse de Paris, 1903, no. 434.

Though the left scapula was slightly winged, the distinctly audible noise was more intense on the left side. This observation is of interest for the reason that in the presence of a winged scapula there must be predicated a weakness of the very muscles which, by apposing the scapula to the wall of the chest, furnish the mechanical basis for snapping. Doubtless the explanation of this case is to be sought in some anomaly of the soft structures. In the absence of more definite findings, however, it must be left in the category of undetermined etiology.

We have had the opportunity of observing several cases belonging to this undetermined group.

Case 1.—A. M., a woman, aged 25, a typist, was seen in the outpatient department in the early part of 1929, complaining of pain in the region of the right shoulder, which was made worse on working. The pain radiated from the right scapular region down the whole right arm, and was associated with a markedly uncomfortable grating sound at the upper angle of the scapula, which could be felt and heard on downward motion of the shoulder girdle. The Wassermann reaction was reported as negative, and x-ray pictures showed no evidence of bony abnormalities. The patient disappeared from our observation before anything could be done.

Case 2.—P. K., a woman, aged 34, a pianist, was first seen in March, 1932, complaining of pain in both forearms. Since the age of 15, she had noted a sense of constriction across the metacarpophalangeal joints on writing and on playing the piano. This sense of tightness was associated with a pain felt mainly along the inner aspect of both forearms and occasionally radiating to the region of the right shoulder and the right middle finger.

Examination disclosed a definite snapping of the scapula on the right side on abduction of the shoulder, with elevation and retraction of the scapula. To a lesser extent, the same was noted on the left side. There was a small area of tenderness over the right pronator radii teres, but no other evidence of neuromuscular involvement. The patient was given diathermy, with no apparent relief, and subsequently disappeared from observation.

The last case is one of more than usual interest because it may throw some light on certain forms of so-called writer's cramp. In an almost identical condition which Galvagni noted, a seamstress of 22 reported that, on attempting to do her work, the fourth and fifth right fingers became extended. There was a loud noise in the region of the inferior angle of the scapula, associated with pain radiating down the neck to the outer side of the arm, and with loss of the power of holding her needle. Examination disclosed an atrophy of the region of the right shoulder, but normal muscular reactions on electrical stimulation. Vesication over the scapula and right shoulder, with a fourteen day period of rest, restored the patient to her normal working capacity. Though unproved, Galvagni was of the opinion that the symptoms might have been attributable to the presence of an abnormally developed bursa in the scapular region, and that many of the cases of occupational cramps associated with pains radiating up the arm were probably to

be explained on this basis. This explanation, however, is purely hypothetic and of interest merely as indicating a method of approach to certain of the cases of occupational cramp associated with scapular grating or snapping.

Excluding these two groups, in which adequate classification is impossible, by far the larger percentage of cases heretofore described can more properly be grouped under the three main divisions noted.

CHANGES IN THE BONY STRUCTURE

In the category of cases due to changes in the bony structure of the scapula or the ribs, a number of subgroups have been noted. The cases in these subgroups may be conveniently divided into those due to:

1. The tubercle of Luschka.
2. Abnormal curvature of the superior angle of the scapula.
3. Exostosis of the ribs or scapula.
4. Tumors of the ribs or scapula.
5. Fracture of the scapula or ribs.
6. Angulation or buckling of the ribs.
7. Tuberculosis or syphilis of the ribs or scapula.

1. The tubercle of Luschka, a small bony or fibrocartilaginous elevation located on the anterior aspect of the superior angle of the scapula, at its largest the size of a pea, usually covered by a bursa, was first described by Luschka [13] and later by von Gruber.[14] Grünfeld found the tubercle present in 7 of a series of 20 cadavers which were selected at random. This percentage, it will be noted, closely approximated the percentage in which he found scapular crepitus in 100 normal people also selected at random, and for this reason he attached great significance to the tubercle as a factor in the production of scapular crepitus. By many, the presence of this tubercle has been considered as solely responsible for the production of snapping of the scapula, especially since resection of this tubercle-bearing area resulted in cure. Heinemann,[15] Volkmann, Lobenhoffer [16] and Huguier [17] each reported cases which would seem to justify this belief. However, in the case which Grünfeld reported, quite the contrary appears to be definitely established. In a woman 32 years old, the pain and noise persisted, even under anesthesia, despite amputation of the tubercle-bearing area, and were obviated only by resection of a strand of the serratus posticus, which was found gray and swollen. The facts in the case would tend

13. Luschka, quoted by Grünfeld.[6]
14. von Gruber: Arch. f. path. Anat. **56**:425, 1872.
15. Heinemann, O.: Klin. Wchnschr. **1**:787, 1922.
16. Lobenhoffer: Beitr. z. klin. Chir. **83**:484, 1913.
17. Huguier, A.: Paris chir. **2**:368, 1910.

rather to support Volkmann [18] and others, who maintained that snapping of the scapula was occasioned by pathologic changes in the scapular musculature rather than by the presence of the tubercle of Luschka. Jastram,[19] too, noted inflammation and degeneration, not only in the region of the tubercle, but at some distance from it, and he expressed the opinion that the snapping resulted from an inequality in the elasticity of the muscle moving over the bursa-covered tubercle, much as a finger plucking a stringed instrument, the chest acting as a resonator. In a case that we observed, we, too, were led to discount the significance of the tubercle.

Case 3.—S. B., a man, aged 25, a plumber, was first seen in the outpatient department on March 4, 1927, complaining of pain in the region of the right shoulder over a period of several months. This pain was associated with a twitching of the right shoulder and a rough grating sound on motion of the right scapula. There was no history of injury. The patient had been receiving baking and massage without any relief.

On examination it was found that the right shoulder was 1½ inches (3.77 cm.) higher than the left. A slight fulness was found in the suprascapular region, along the upper border of the scapula. There was a slight local tenderness on pressure over this region. There was no limitation of motion in the right shoulder joint, but a marked grating sound was found on downward motion of the shoulder girdle. The posterior edge of the deltoid on the right side was markedly prominent, and there was a continuous fibrillar contraction of the long head of the triceps and deltoid, with marked tenderness over the right trapezius muscles. The patient was given diathermy, roentgen therapy, salicylates, quinine and injections of urea hydrochloride, without relief.

In January, 1931, the patient still complained of needle-like pains in the lower cervical, upper dorsal spine, and especially between the shoulder blades. There was marked crepitation on motion of both scapulae. X-ray pictures showed what appeared to be distinct, rounded, tubercle-like thickening of the upper angle of the scapula. The Wassermann reaction was negative.

When seen in May, 1932, the grating was still present, but the sound produced was not definitely localized to the region of the tubercle and gave the impression of soft tissue crepitus rather than that caused by the rubbing together of two bony surfaces. The patient refused operation and is still under observation.

From what has gone before, it would appear that there is a marked divergence of opinion as to the real importance of the tubercle of Luschka. As in other controversial matters, the truth in all probability lies somewhere in the middle ground. Doubtless there may be some cases in which the removal of the tubercle areas resulted in relief of symptoms. On the other hand, we are supported by competent roentgenologic authority in the opinion that the tubercle exists in a far greater percentage of cases than the presence of symptoms would indi-

18. Volkmann, J.: Klin. Wchnschr. **1**:1838, 1922.
19. Jastram, M.: Deutsche Ztschr. f. Chir. **165**:309, 1921.

cate. And in such event, the conclusion naturally presents itself that the tubercle, even when present, may be of only coincidental significance.

2. The second subdivision is that in which abnormal forward bending of the superior margin of the scapula has been noted. This is apparently of congenital origin, though Lotheissen expressed the opinion that it may be due to the continuous, strong pull of the anterior serratus muscles. The significance of the anterior serratus muscles can easily be demonstrated. In cases of Sprengel's deformity, forward bending of the superior border of the scapula is not unusual, yet it is extremely uncommon to have true snapping of the scapula because of the winging of the scapula. In one case which we had the opportunity of observing, this was clearly shown.

CASE 4.—E. M., a woman, aged 22, who was seen in November, 1929, had first noted weakness of the right shoulder and arm three or four years previously. Within the past two or three weeks she began to complain of a sensation of pain in the left arm and inability to abduct either arm to a right angle.

Examination disclosed a patient of typical acromegalic facies, with moderate exophthalmos. Both arms could be abducted to about 75 degrees. Both scapulae were high and smaller than normal, measuring only 7 inches (17.78 cm.) from the superior to the inferior angle, and presented a marked forward curvature of the superior angles. There was a definite weakness, associated with atrophy, in the right hand, as compared with the left. All deep reflexes of the right extremity were absent, but sensation was apparently normal. As the arms were brought to their limit of abduction, a definite winging of the scapula, due to weakness of the anterior serratus muscle, became apparent. With the arms in the forward position, they could be readily abducted passively throughout the whole range of normal motion, but when the arms were retracted backward, or when the scapulae were pressed against the sides of the chest before attempting abduction, a marked snapping sound, such as is made when running a stick along the stakes of a picket fence, could be heard and felt. At one of the larger neurologic hospitals in the city, a diagnosis of amyotrophic lateral sclerosis was made. In view of the associated neurologic condition no treatment was undertaken.

This case is presented because it may serve almost as a laboratory experiment in elucidating the mechanics of snap production in the usual clinical case. The mechanism of snapping in this case is apparent: a forwardly bent, superior, scapular margin brought firmly in contact with the posterior surface of the ribs, by an external pressure, simulating the action of a normal serratus anticus muscle. The same mechanism may be assumed in the cases reported by Lotheissen, Küttner,[20] de Beule [21] and Schoemaker [22] and in case 5.

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20. Küttner, H.: Deutsche med. Wchnschr. **30**:534 and 580, 1904.

21. de Beule, in discussion of Hendrix: J. de Chir. et ann. Soc. belge de chir. **7**:120, 1907.

22. Schoemaker, J.: Nederl. tijdschr. v. geneesk. **2**:744, 1917.

CASE 5.—T. R., a girl, aged 18, was seen in the outpatient department of the Hospital for Joint Diseases in February, 1932, complaining of pain radiating down the left shoulder. Three years previously, while running a foot race, she had fallen on her left shoulder and suffered a fracture of the left clavicle, for which she had received inadequate treatment. As a result, she was left with a malunited fracture of the outer end of the left clavicle, and since that time had noticed occasional pain in the left scapular region, with winging of the scapula. There appeared to be no limitation of the left shoulder in any direction.

Examination disclosed the malunited fracture of the left clavicle, which, however, was apparently entirely symptomless. On motion of the shoulder a definite snapping sound was heard and felt in the left scapular region on abduction of the shoulder. The left scapula could easily be heard to make two separate jumps or snaps, with increasing abduction of the shoulder. To our surprise, though the patient complained of no symptoms whatsoever, an almost identical condition was found in the right shoulder, to which no accident had occurred. On the left side

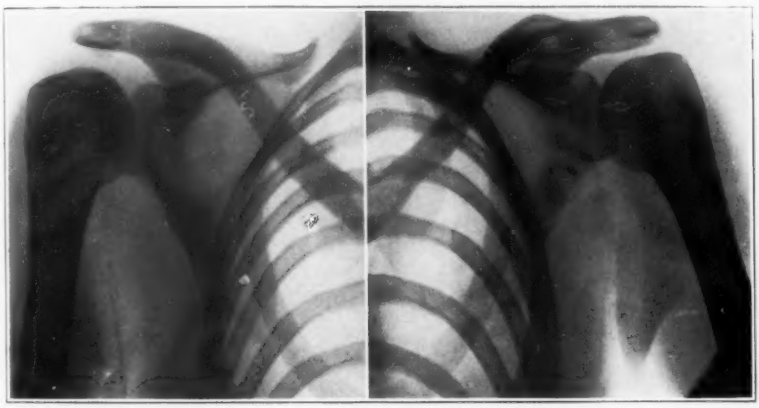

Fig. 1 (case 5).—Roentgenograms, showing bilateral forward curvature of the superior scapular edge, with marked varus of the humeral head.

flexion to 120 degrees, extension to 20 degrees and abduction to 90 degrees produced the sound, while on the right side flexion to 110 degrees, abduction to 90 degrees and even the slightest degree of extension caused the sound to become apparent. The etiologic factor in this case was immediately made apparent on a close study of x-ray pictures of both shoulders. Both showed a marked increase in the normal forward curvature of the superior angle of the scapula, with a peculiar conformation of the humeral head, which will be discussed briefly later (fig. 1).

On February 25, an oblique incision was made over the superior angle of each scapula, and the supraspinous portion of the scapula, from the vertebral border to the superior scapular notch, was resected subperiosteally. The wounds healed well, and motion was begun immediately after subsidence of pain. The resected portions of both scapulae (fig. 2) showed nothing unusual on gross and microscopic examination. Within a period of two weeks the patient was discharged from the hospital, apparently completely cured, but about two months later she returned, complaining of slight pain only in the right scapular region. Examination disclosed

the complete disappearance of the snapping sound previously heard and its replacement by a definite grating crepitus, determinable only by palpation. This yielded readily to the application of diathermy and massage.

Clinically, forward curvature of the superior angle, when present in an abnormal degree, may be demonstrated by grasping the lower end of the scapula, forcibly retracting it from the wall of the chest and then palpating along the upper portion of the vertebral border. When the curvature itself cannot actually be felt, an impression of increase in the thickness of the superior angle may be obtained, which can then be checked by x-ray pictures. Roentgenographically, we have best been able to demonstrate the condition by oblique views of the shoulder. In such an angle, the abnormal forward bending of the superior margin can best be seen. But even when this cannot definitely be determined,

Fig. 2.—Supraspinous portions of the scapula, removed at operation.

other evidence may be at hand. Attention has been called to the fact that an abnormal curvature may be suspected when the line of the superior margin of the scapula tilts downward toward the glenoid fossa and makes a sharply acute angle with the line of the superior margin of the acromion and spinous process of the scapula, instead of being nearly parallel with it.

Case 5 appeared to be of more than usual interest for several reasons. It demonstrated quite conclusively the significance of the increased curvature of the upper portion of the scapula in the production of snapping, with the subsidence of symptoms following removal of the offending portions of bone. It was of interest further in that the patient presented two types of scapular sound, one of which was to be explained on the basis of the anomalous curvature noted in the superior angle of the scapula, the other of which developed after operation and was, we believe, of an entirely different nature. The

latter sound was in the nature of a soft tissue crepitus, appeared only after operation and disappeared so promptly after the use of diathermy that we believed it to be of the nature of a postoperative traumatic myositis. In this sense it is probably to be grouped with those types of scapular crepitus due to changes in the muscles and will be discussed later.

Finally, this case seemed to us to be of unusual interest, especially to those practicing industrial surgery. It will be noted that the patient correlated and causally connected the snapping with an injury suffered some time previously. Our patient was a young lady of average intelligence and not at all contentious in a medicolegal sense. Still, she assumed, without doubt, that the snapping noise to which her attention was drawn only after the injury to her shoulder was causally related to that injury. A patient need be neither a malingerer nor a neurotic person to infer, incorrectly, a causal relationship between these two coincidental phenomena. Yet, if the patient is either neurotic or a malingerer, it is readily apparent that some difficulty might be experienced in disposing of the case in an equitable manner. To prevent such unpleasantness, x-ray pictures should be taken immediately after the accident. Since the scapular crepitus associated with injury is of the type in which a fracture with malposition of the scapula or the ribs occurs, it is obvious, even in the absence of roentgen findings, that the snapping should be unilateral and localized to the side on which the alleged injury had occurred. In cases in which the snapping is bilateral, the correlation of snapping with the injury should not be entertained. Lotheissen called attention to this point and stressed it, especially in view of the fact that scapular crepitus might be voluntarily produced by a patient intent on a legal suit.

Another case in which scapular snapping associated with forward bending of the superior border was present, but in which the etiology of the snapping could not be definitely determined because operation was not performed, is added for the sake of completeness.

Case 6.—R. L., a woman, aged 40, a dressmaker, was seen in the outpatient department in February, 1932, complaining of pain in the right scapular region, which radiated down to the right hand. This pain had appeared at irregular intervals during a period of four years. Each attack lasted three or four days at a time and was apparently relieved by diathermy.

The Wassermann reaction was negative. A roentgenogram of the shoulder girdle (fig. 3) suggested a definite increase in the forward angulation of the superior angle of the scapula. There was no limitation of motion in the shoulder, but backward extension of the shoulder and abduction of the right upper extremity caused a mild grating sound, which could be felt and heard in the region of the superior angle. The left scapula was apparently normal. Resection of this portion of the bone was suggested to the patient, but she demurred, and has since disappeared from our observation.

3. The third subdivision is that in which scapular snapping is noted in the presence of exostoses on the ribs or on the undersurface of the scapula. Some authors seem to think that there is no definitely established relationship between the presence of an exostosis and the development of scapular snapping. However, Demarquay,[23] Zieschang,[24] McWilliams,[25] Betke, Brown,[26] Goldthwaite,[27] Görres [28] and others have reported cases in which removal of the portion of the scapula bearing the exostosis resulted in cure of the condition. The exostosis may

Fig. 3 (case 6).—Roentgenogram, showing forward angulation of the superior scapular margin.

be found either at the superior or at the inferior angle of the scapula and may vary in size from osteocartilaginous nodules to relatively large mushroom-shaped masses.

23. Demarquay, quoted by Küttner;[20] quoted by Grünfeld.[6]

24. Zieschang, Karl: Ueber das Scapularkrachen, Leipzig, B. Georgi, 1907; quoted by Ssoson-Jaroschewitsch, A. J.: Arch. f. klin. Chir. **123**:378, 1923.

25. McWilliams, C. A.: Scapular Exostosis with Adventitious Bursa, J. A. M. A. **63**:1473 (Oct. 24) 1914.

26. Brown, L. T.: Boston M. & S. J. **174**:652, 1916.

27. Goldthwaite, quoted by Brown.[26]

28. Görres, H.: Deutsche med. Wchnschr. **47**:897, 1921.

4. Benign tumors of the ribs or of the scapulae do not ordinarily produce scapular snapping, though Habermann [29] reported 2 cases, in 1 of which a chondroma and in the other of which an osteochondroma were found. Bloch [30] reported a case in which the nature of the tumor was not stated. No cases of malignant tumors have been reported as producing snap formation.

5. Other causes which have resulted in anomalous relationships of the bony structures with consequent sound production have been observed. Fracture of the scapula, producing a snapping easily audible at a distance of 9 feet (274.3 cm.), was reported by Favier.[31] Gaujot [32] reported a case in which a fracture of the scapula was followed by the formation of a large bursa. Terrillon reported a similar case in which a hygroma, containing rice bodies, developed under the scapula following a fracture of the ribs. Whether these cases are to be given absolute credence is doubtful, since they all occurred in the preroentgen era.

6. The association of snapping with angulation or buckling of the ribs, as is found in scoliosis, has been reported by Volkmann (2 cases) and Jacoby.

7. Trélat and Peré [33] reported cases in which the snapping was believed to be due to syphilis. In Trélat's case the voluminous subscapular tumor receded in size under antisyphilitic treatment. Galvagni reported 2 cases, Walther [5] 1 case and Lemoine [34] another case in which tuberculosis was considered the underlying etiologic factor. In these cases, either primary caries of the ribs, with or without cold abscess formation, or undue prominence of the ribs as a result of secondary deformity of the chest has been held responsible for the sound formation.

CHANGES IN THE MUSCULATURE

The second main group in which scapular crepitus has been noted is that associated with changes in the muscles lying between the scapula and the ribs. Here, too, a number of explanations have been suggested by different authors. Mention has already been made of the opinion of Jastram as to the significance of inflammatory changes in the muscles. Voelcker [35] suggested that a lesion in the muscle similar to tendonitis crepitans might be responsible for this type of snapping. The crepitus noted after operation in case 5 may in some respects be considered as substantiating this opinion. On the other hand, it must be admitted

29. Habermann, R.: Berl. klin. Wchnschr. **48**:612, 1911.
30. Bloch, O., quoted by Jacoby.[10]
31. Favier, H.: Gaz. d. hôp. **67**:1108, 1894.
32. Gaujot, quoted by Küttner;[20] quoted by Huguier.[17]
33. Peré: J. d. mal. cutan. et syph. **11**:133, 1899.
34. Lemoine, in discussion of Hendrix: J. de chir. et ann. Soc. belge de chir. **7**:120, 1907.
35. Voelcker, quoted by Volkmann.[18]

that it would be extremely difficult to prove this hypothesis unless widespread incision and examination were made at the time of operation. In most cases these measures are impossible, and simple microscopic changes of lesser degree, in our opinion, cannot be accepted as in any measure satisfactory evidence.

Ledentu,[36] Testut [37] and others have pointed out that not degenerative or inflammatory conditions, but rather anatomic variations of muscles, such as the anterior serratus, are to be held responsible for the production of sound. They have observed that not uncommonly fasciculi of the anterior serratus muscle may be wanting and that the interspace between the digitations may be covered by a thin connective tissue layer. As a consequence of this, sounds may be produced either by the snapping of the free edge of one of these digitations over the angle of the scapula, or by the rubbing of the uncovered scapula against the ribs at its inferior angle. Terrillon and Zaphiriadès each reported a case which they believed bore out the former of these two suggestions, but since no further details are given, the cases must be accepted with some reservation. Terrillon reported 3 other cases in which he believed the latter of the two hypotheses to be effective. The observations were made in 3 patients in whom, following ankylosis of the shoulder, a marked atrophy of the scapular muscles occurred. To this both Terrillon and Mauclaire, who reported a similar case, attributed the production of sound.

In regard to the former of these two hypothetic explanations, we are unable to express any opinion, but as to the latter, it may be doubted on purely a priori grounds. In the first place, it must be apparent that when ankylosis of the shoulder had occurred, hypertrophy rather than atrophy of the serratus would be expected. But even if atrophy were present, winging of the scapula, with a consequent absence of snap formation, as was shown in case 4, should be noted. In the second place, it would seem that with the relatively large number of ankyloses at the shoulder, produced either artificially or accidentally, some mention would have been made of the appearance of this phenomenon by other authors. Since snapping of the shoulder does not ordinarily occur following ankylosis of the shoulder, it is our opinion that forces other than those suggested must be at work.

CHANGES IN THE BURSAE

The third main group is that in which scapular snapping has been attributed to the presence of normal or adventitious bursae. Normally, two bursae are present beneath the scapula; the one at the upper angle

36. Ledentu, quoted by Huguier.[17]

37. Testut, quoted by Ssoson-Jaroschewitsch, A. J.: Arch. f. klin. Chir. **123**: 378, 1923.

(bursa mucosa angulae superioris scapulae) is situated in the depths of the anterior serratus muscle, and is present about once in every 8 persons examined. The other, somewhat rarer (bursa mucosa serrata), is found in the connective tissue between the anterior serratus muscle and the upper part of the lateral wall of the chest.

Growth of these bursae, especially of the thick-walled, rice-filled variety, has been considered a factor in the production of scapular snapping. Camus [5] described such a case found at autopsy, as did Galvagni and others. Hendrix [38] reported a case in which he believed the sound was caused by an inflammation in one of the subscapular bursae, while Jacoby reported a case in which the x-ray picture showed two irregular shadows beneath the level of the scapular spine. These he considered to be calcium deposits in the bursa subscapularis. We have seen no similar case.

In the foregoing part the clinical characteristics of this condition have been sufficiently emphasized to require no further reiteration. To a large extent the therapy, too, has been indicated in its general outlines. It may, however, be advisable to review briefly the procedures which have been recommended in the treatment of this condition. Both surgical and nonsurgical procedures have been described. In general conservative measures have been of value only in those cases in which changes in the soft structures were suspected. Terrillon obviated the symptoms in one of his patients by the fashioning of a brace designed to limit the motion of the scapula without interfering with the function of the shoulder. In another case he drained the subscapular bursa, with subsequent infection and death. No autopsy was obtained. In some cases, simple counterirritation, as by vesication in the case reported by Galvagni, has given satisfactory results. In other cases physical therapy and massage have been of value. Mauclaire performed a muscle plastic, by reflecting a quadrangular flap of the rhomboids or of the trapezius and suturing it to the undersurface of the scapula, where it was presumed to act as a cushion, protecting against abnormal rubbing of the scapula against the wall of the chest. Though this procedure seems to have given satisfactory results in several cases, it has been criticized by others on the ground that the reflected muscle flap promptly deteriorated and was replaced by a thin, atrophic layer of connective tissue, which defeated the original purpose of the operation. Where there have been definitely demonstrable bony changes, an effort has been made to remove the cause of operation. In some cases the superior and in other cases the inferior angle of the scapula has been resected. In our case and in several others reported in the

38. Hendrix: J. de chir. et ann. Soc. belge de chir. **7**:120, 1907.

literature the upper margin of the scapula was amputated, while in still others angulated portions of ribs or scapula were removed, with some success.

SUMMARY OF SNAPPING SCAPULA

An unusual syndrome has been described, the chief feature of which is the production of a snapping sound on motion of the scapula. The etiology is varied. For the most part, only conservative treatment need be instituted, but when there are definite bony changes, as, for example, excessive forward bending of the scapula and exostosis, surgical removal of the offending part should be undertaken.

HUMERUS VARUS

During the course of the roentgenographic examination in case 5 we were struck by the peculiar conformation of the head of both humeri. Figure 1 shows quite characteristically the extreme downward bending of the head of the humerus, analogous to the condition found more commonly in coxa vara. The head appeared in no way malformed, but the glenoid appeared to be definitely smaller than normal and to project outward like a nipple. The neck appeared markedly shorter and its angle with the head and shaft of the humerus much decreased. The plane of the anatomic neck, instead of being oblique, became almost vertical, and, on the left side, the level of the upper edge of the great tuberosity was definitely higher than the head of the humerus. There was no evidence, either clinically or roentgenologically, of any interference in the motions of the shoulder joint. Roentgen examination of other parts of the bony skeleton revealed no similar lesion, and we believe we are justified in excluding any systemic condition such as rachitis or achondroplasia.

This condition has been called humerus varus and was first described by Riedinger [39] in 1900. Since then a number of articles on the subject have appeared in the Swiss and Italian literature, but nothing at all as yet in the English literature. Humerus varus in general is characterized by a high position of both the great tuberosities in relation to the head of the humerus, by a diminution in the radius of the curvature of the humerus, by a change in the angle of the neck, by a shallowness in the depression normally found between the head and the anatomic neck of the humerus and by the more vertical position of the anatomic neck of the humerus. In the few cases which have been examined pathologically (Bircher), the humerus showed an absence of its normal structure, the spongiosa being narrow and irregular, and the marrow presenting a peculiar foamy consistency.

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39. Riedinger, J.: Deutsche Ztschr. f. Chir. **54**:565, 1900; Kongr. d. deutsch. Gesellsch. f. orthop. Chir. **3**:317, 1909.

Nicotra,[40] whose article presents an excellent bibliography on the subject, divided humerus varus into two groups, false humerus varus and true humerus varus.

False humerus varus may be due to a number of factors, such as fracture of the anatomic or surgical neck of the humerus. Some have considered that this type should be characterized by a special designation, such as humerus varus adductus. Other cases have been reported in which humerus varus has been noted in arthritis and in tumor formation, with consequent malacia of the bone, and Riedinger reported a case in which a humerus varus of 100 degrees was found in a case of ankylosis of the elbow. This varus development Riedinger considered as being an adaptive mechanism to accommodate for the ankylosis of the elbow. In general, this type of varus causes an interference with motion of the shoulder joint, compatible with its underlying pathologic changes. Little attention has been focused on it.

Nicotra has subdivided true humerus varus into two main types: humerus varus dystrophicus and humerus varus adolescentium (cysticum). In the former, or dystrophic, group may be placed the type of varus seen in rickets (Riedinger), in cretinism and in chondrodystrophy (Bircher). In these cases the varus deformity is, of course, secondary to general dystrophic changes in the skeleton. Bircher [41] has described several anatomic specimens obtained from cretins, in which he noted flattening of the head, a reduction in the angle of inclination of the neck of between 20 and 40 degrees, a decrease in the directional angle of the neck of the humerus, a decrease in the radius of the curvature of the head, an elevation of both greater and lesser tuberosities of the humerus and an inward torsion of the upper part of the shaft of the humerus. No characteristic changes have been noted in the glenoid cavity, though in 1 case Haumann [42] described changes similar to those seen in epiphysitis. The muscular insertions, especially the cristae of the intertuberculous sulcus, are prominently developed. The changes observed in the cretin have also been seen in microcephalic dwarfs, in achondroplasia and, occasionally, it has been said, in rickets. Some have considered the changes as a reversion to type, such as is usually seen in anthropoid apes and in human embryos. Bircher has attributed them to the general dystrophic changes with late walking and consequently prolonged creeping during infancy. As a result of this, the weight of the trunk on the arms and the excessive pull of the deltoid have been thought to lead to humerus varus. The condition is symptomless, produces no limitation of motion, gives no discrepancy in the relative length of the arm and requires no treatment.

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40. Nicotra, A.: Clin. chir. **33**:914, 1930.

41. Bircher, E.: Deutsche Ztschr. f. Chir. **96**:598, 1908; Fortschr. a. d. Geb. d. Röntgenstrahlen **16**:325, 1911.

42. Haumann, W.: Beitr. z. klin. Chir. **140**:136, 1927.

Humerus varus adolescentium (cysticum), on the other hand, is an unusual clinical entity, originally described by Stropeni [43] and subsequently by Nicotra. It usually occurs in the second decade of life and is characterized by apparent subluxation of the head. There is definite limitation of abduction, with shortening of the arm, even up to 8 or 10 cm. Pain may or may not be present. The x-ray pictures are distinctive, and since no pathologic material is at hand, they afford the only means of etiologic interpretation. The varus occurs in the surgical neck, at the junction of the metaphysis and diaphysis. The epiphyseal line may show early consolidation. The diaphysis at its uppermost part is much thinned and usually contains on its medial aspect what is interpreted as a solitary cyst, through which pathologic fracture may occur. The head of the humerus, slightly reduced in size, but otherwise normal, fits within the deepened groove or depression (insaccatura) made by the cyst. There is a displacement of both tuberosities upward, with a marked decrease in the angle of inclination, even up to 50 degrees. To a lesser extent there is a change in the directional angle, but torsion of the humerus is not evident.

Nicotra noted that humerus varus adolescentium is observed only in cases of this solitary type of cyst, and never in cases of multiple cysts of the humerus. The explanation adduced by Nicotra is ingenious; it still needs confirmation. Seiffert,[44] on the other hand, described a case which falls in this group, but he attributed it to a questionable injury sustained at birth.

The number of cases thus far described is small, not more than 11 having been noted. Except when there is a definite limit of abduction at the shoulder, no treatment is necessary. Anglesio [45] is the only one who until now has attempted osteotomy of the upper part of the humerus for the purpose of correction of the varus deformity.

The case which we reported (case 5) does not seem to fit into any of the classifications previously mentioned, and we have the feeling that it belongs in the group which may be termed congenital humerus varus. Such a classification has previously been suggested, but no case has heretofore been described. We have no doubt that were closer attention to be paid to the variation in the angle of the neck of the humerus, numerous similar cases might be brought to light. Since practically the only means of diagnosis in these cases is by the x-rays, some attention should be paid to the technic of taking x-ray pictures. Köhler [46] noted that in the prone position varus of the humerus may be simulated, even in the normal arm. For the purpose of obviating these difficulties,

43. Stropeni, L.: Chir. d. org. di movimento **12**:531, 1928.

44. Seiffert, J. L.: Fortschr. a. d. Geb. d. Röntgenstrahlen **43**:620, 1931.

45. Anglesio, B.: Arch. di ortop. **46**:417, 1930.

46. Köhler, Alban: Röntgenology, translated from the German by Arthur Turnbull, New York, William Wood & Company, 1928, p. 72.

Preisser[47] suggested that the x-ray picture be taken with the arm externally rotated and somewhat abducted. No treatment is, of course, necessary in this type of case, since usually no symptoms exist.

ADDENDUM

We have recently been fortunate in being able to reexamine a patient suffering from Gaucher's disease in whom marked changes in the skeletal system were observed. Since this is the first, if not the only, case in which a humerus varus has been observed in Gaucher's splenomegaly, we feel justified in briefly presenting the x-ray photographs taken in this case.

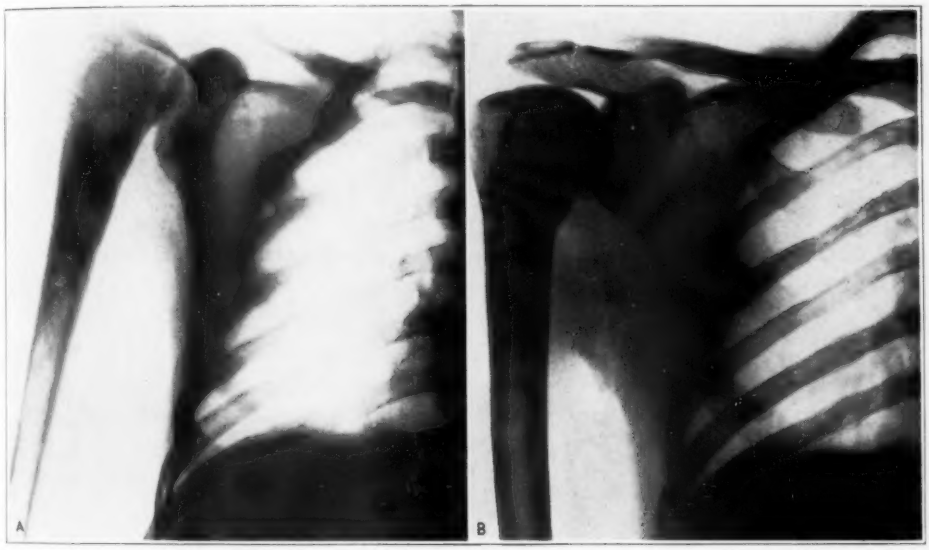

Fig. 4.—*A*, roentgenogram taken in 1927; *B*, one taken in 1932.

A fairly complete discussion of the bone changes was previously published,[48] and the reader is referred to that article for the more intimate details of the patient's condition. For purposes of comparison, the x-ray photograph of the findings observed in the right shoulder in 1927 is herewith reproduced (fig. 4 *A*). Apart from the characteristically mottled appearance of the bone, it will be observed that the angle of the neck of the humerus is quite normal. If the x-ray photograph of the patient's shoulder made in 1932 is examined (fig. 4 *B*), it will be seen that the angle of the neck is markedly decreased, so that this patient has a true humerus varus.

47. Preisser, G.: Fortschr. a. d. Geb. d. Röntgenstrahlen **12**:3, 1908.

48. Milch, H., and Pomeranz, M.: Bone Changes in Gaucher's Splenomegaly, Ann. Surg. **89**:552 (April) 1929.

As was previously noted, Bircher attributed the development of humerus varus in the rachitic cases which he examined to a prolonged period of creeping. However, in this case this factor can be completely eliminated as part of the causative mechanism of the humerus varus. It must be presumed, then, that the distorting forces are to be found in the muscles of the shoulder joint acting on a neck in which the normal tensile strength had been reduced as a result of the displacement of osseous tissue by an infiltration of Gaucher's cells.

ADDITIONAL BIBLIOGRAPHY

Allison, N.: S. Clin. North America **2**:1541, 1922.
Angeletti, E.: Chir. d. org. di movimento **3**:513, 1919.
Chulkoff, I.: Med. Obozr., Mosk. **71**:104, 1909; quoted by Jacoby, P.: Ugesk. f. læger **84**:1071, 1922.
Ewald, P.: Ztschr. f. orthop. Chir. **28**:166, 1911.
Fick: Abhandl. d. k. preuss. Akad. d. Wissensch.; quoted by Seiffert, J. L.: Fortschr. a. d. Geb. d. Röntgenstrahlen **43**:620, 1931.
Giovetti: Atti d. IV Cong. ital. di radiol. med., 1922.
Kerr: Proc. Path. Soc., Philadelphia **1**:34, 1860.
Lange, F.: Lehrbuch der Orthopädie, ed. 3, Jena, Gustav Fischer, 1928, p. 427.
Lewin, H.: Röntgenpraxis **3**:556, 1931.
Merlini, A.: Radiol. med. **9**:265, 1922; Chir. d. org. di movimento **6**:329, 1922.
Mezzari, A.: Arch. di radiol. **4**:100, 1928.
Nicolis, S.: Radiol. med. **10**:277, 1923.
Pouzet and Labry: Lyon méd. **143**:166, 1929.
Richet: France méd. **1**:460, 1885.
Rocher, H. L., and Rondil, G.: Arch. franco-belges de chir. **32**:524, 1930.
Rosaire, E.: Contribution à l'étude de l'angle de déclinaison de l'humérus à l'état normal et à l'état pathologique, Thèse de Lyon, 1892, no. 749.
Sappey, quoted by Anglesio, B.: Arch. di ortop. **46**:417, 1930.
Satta, F.: Chir. d. org. di movimento **11**:57, 1926.
Signorelli, A.: Boll. d. Soc. lanciscana d. osp. di Roma **25**:64, 1905.
Steindler, A.: Reconstructive Surgery of the Upper Extremity, New York, D. Appleton and Company, 1925, p. 7.
Westcott, H. H.: J. Bone & Joint Surg. **7**:469, 1925.
Zucchi, A.: Arch. di ortop. **2**:108, 1885.

EFFECTS OF CHOLECYSTECTOMY ON THE BILIARY SYSTEM

A MORPHOLOGIC STUDY IN THE DOG

BÉLA HALPERT, M.D.
NEW HAVEN, CONN.

ALLAN G. REWBRIDGE, M.D.
MINNEAPOLIS
AND
CLAIRE HEALEY, M.D.
CHICAGO

Opinions still differ regarding the effects of surgical removal of the gallbladder on the rest of the biliary system. The clinical importance of this matter urged us to a reinvestigation. It soon became evident, however, that the problem was too complex to be considered as a whole, and for that reason we chose to confine our investigation in the dog to merely one phase, namely, the morphologic.

In reviewing the literature, we learned that cholecystectomy is an operation three hundred years old. It was first performed on a dog in 1630 by the Italian Zambeccari. The first cholecystectomy on man was performed by Langenbuch [1] in the "Lazaruskrankenhaus" of Berlin on July 15, 1882. The history of cholecystectomy is vividly presented, and the views regarding the effects of such a procedure are critically reviewed in Rost's [2] paper of 1913. The problem has since been approached experimentally by a number of investigators, notably by

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From the Departments of Pathology and Surgery, the University of Chicago, and the Department of Surgery, Yale University School of Medicine.

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1. Langenbuch, C.: Chirurgie der Leber und Gallenblase, Stuttgart, Ferdinand Enke, 1894 and 1897.

2. Rost, F.: Die funktionelle Bedeutung der Gallenblase: Experimentelle und anatomische Untersuchungen nach Cholecystectomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:710, 1913.

Lapenta,[3] Judd and Mann,[4] Eisendrath and Dunlavy,[5] Hartman, Smyth and Wood,[6] Gohrbandt,[7] Mairano,[8] Canavero,[9] Troitzky [10] and Sutton.[11]

Lapenta (1916) made a gross examination of the extrahepatic biliary system of "about" ten dogs, from twenty to sixty days following cholecystectomy. The extrahepatic biliary ducts were dilated in all his animals. In two the cystic stump dilated "in a bulb fashion."

Judd and Mann (1917) studied the effects of cholecystectomy on the dog (also on the cat and the goat). Their conclusions, however, that "after removal of the gallbladder all of the ducts outside the liver dilate" and that "the sphincter at the entrance of the common bile duct into the duodenum is the chief factor in producing this dilatation" are not convincingly supported by morphologic evidence.

Eisendrath and Dunlavy (1918) investigated the fate of the cystic duct following removal of the gallbladder in a number of dogs opened from one week to six months after cholecystectomy. They noted a progressive dilatation of the cystic duct.

Hartman, Smyth and Wood (1922) cholecystectomized nine dogs. In eight of these they retained from 6 to 20 mm. of the cystic duct, and in one none. The animals were reopened from six to fourteen weeks later. The extrahepatic biliary ducts were somewhat dilated in all; the cystic stumps, when retained, dilated to 1 cm. in diameter and elongated to from 1.2 to 2.5 cm. The microscopic structure of these stumps resembled that of a gallbladder and showed no evidence of thinning or stretching.

Gohrbandt (1927) experimented on dogs, removing the whole of the cystic duct at cholecystectomy in one series, retaining it in another, and retaining also the neck of the gallbladder in a third. In the first

3. Lapenta, V. A.: Is the Gallbladder a Useless and Functionless Organ? Interstate M. J. **23**:993, 1916.

4. Judd, E. S., and Mann, F. C.: The Effect of Removal of the Gall-Bladder, Surg., Gynec. & Obst. **24**:437, 1917.

5. Eisendrath, D. N., and Dunlavy, H. C.: The Fate of the Cystic Duct After Cholecystectomy: An Experimental Study, Surg., Gynec. & Obst. **26**:110, 1918.

6. Hartman, F. L.; Smyth, C. M., Jr., and Wood, J. K. W.: The Results of High Ligation of the Cystic Duct in Cholecystectomy, Ann. Surg. **75**:203, 1922.

7. Gohrbandt, E.: Gibt es eine Neubildung der Gallenblase? Arch. f. klin. Chir. **145**:286, 1927.

8. Mairano, Mario: Le modificazioni delle vie biliari dopo la colecisectomia, Arch. ital. di chir. **20**:468, 1928.

9. Canavero, Michelangelo: L'influenza della colecistectomia sulle vie biliari, Policlinico (sez. chir.) **35**:429, 1928.

10. Troitzky, A. A.: Changes in Liver and Biliary Tract After Excision of Gallbladder, Omsky med. j. **4**:21, 1929.

11. Sutton, J. E., Jr.: Changes in the Intrahepatic Bile Ducts Following Cholecystectomy, Ann. Surg. **91**:65, 1930; abstr., Arch. Path. **9**:764 (March) 1930.

series of four dogs, reexamined one, two, three and four months following the operation, no regeneration of the cystic duct occurred, nor was there any dilatation at its site. In his second series of four animals, a bulblike distention of the retained cystic duct was noted one, two, three, four and five months following the operation. The microscopic structure of the stump was that of a dilated cystic duct and not that of a gallbladder. In three additional dogs the same procedure was repeated, and with the idea of injuring the cystic stump the peritoneal covering of the cystic duct was stripped. In these animals a more marked dilatation of the cystic duct occurred than in the previous series. The distention stopped at the junction of the cystic duct and the ductus choledochus. In five dogs, in which the resected end of the cystic duct was properly cared for, i. e., the peritoneum was closed over the stump, no dilatation of the cystic duct occurred. In three dogs of the third series, a small portion of the gallbladder was retained together with the cystic duct. These, when examined two, four and six months, respectively, following the cholecystectomy, showed a gallbladder about half the size of the original. No mention is made by Gohrbandt of any dilatation of the hepatic and common bile ducts following these procedures.

Mairano (1928) studied the biliary system of seven dogs, 12, 40, 90, 120, 150, 240 and 390 days following cholecystectomy. He observed dilatation of the extrahepatic biliary ducts in all of his animals, illustrating his findings with roentgenograms. The cystic duct, retained in two of his dogs, revealed normal microscopic structure in spite of the gross enlargement.

Canavero (1928) made morphologic studies on the biliary system of eight dogs from fifteen days to fifteen months following cholecystectomy. In his first group of two animals, no significant gross or microscopic changes were noted in the extrahepatic or intrahepatic biliary ducts fifteen days following removal of the gallbladder. In his second group of three animals, thirty-five, sixty and ninety-six days following cholecystectomy, dilatation of the extrahepatic biliary ducts occurred with an increase in size of the cystic stump. The microscopic changes described were neither definite nor characteristic. The morphologic changes in the third group of three animals, ten, fourteen and sixteen months following cholecystectomy, were about the same as in the second group. Canavero concluded from these experiments that the changes in the biliary system occur within one month following removal of the gallbladder.

Troitzky (1929) removed the gallbladders of seven dogs. Microscopic examination of the liver four months following the operation

showed a chronic inflammation. The extrahepatic biliary ducts were dilated. There was no evidence of a tendency to the formation of a new gallbladder.

Sutton (1930) removed the gallbladders of eighteen dogs. From fifteen to seventy-seven days after this cholecystectomy he injected a 12 per cent solution of silver gelatin through the common bile duct under a pressure of from 100 to 180 mm. of mercury and placed the specimens in an ice-cold 5 per cent solution of formaldehyde. The same procedure of injection and fixation was carried out in six normal dogs. Subsequent microscopic studies showed that in the control ani-

Effects of Cholecystectomy on the Extrahepatic Biliary Ducts of the Dog

Dog	Sex	Weight, Kg.	Duration of Experiment, Weeks	Appearance of Extrahepatic Biliary Ducts at Close of Experiment		
				Gross	Microscopic	Cystic Stump
C-13	♀	16	1	Normal	Normal	Not dilated
C-14	♀	8	1	Normal	Normal	
C-7	♂	8	2	Normal	Normal	Not dilated
C-8	♂	10	2	Dilated	Dilated	Not dilated
C-10	♂	12	3	Dilated	Dilated	
C-9	♂	17	4	Normal	Normal	Not dilated
C-16	♂	8	4	Normal	Normal	Not dilated
C-11	♂	13	5	Normal	Normal	Not dilated
C-12	♂	10	5	Dilated	Normal	
C-17	♂	9	6	Dilated	Dilated	Dilated
C-18	♂	8	6	Normal	Normal	Not dilated
C-19	♀	9	8	Normal	Normal	Not dilated
C-20	♂	10	8	Normal	Normal	Not dilated
C-5	♀	8	10	Normal	Normal	Not dilated
C-6	♂	14	10	Dilated	Dilated	Not dilated
C-4	♀	13	11	Dilated	Normal	Not dilated
C-3	♂	16	12	Dilated	Normal	Not dilated
C-21	♀	9	12	Dilated	Normal	Not dilated
C-1	♂	10	16	Normal	Normal	Not dilated
C-22	♂	12	16	Dilated	Dilated	
C-23	♀	7	20	Dilated	Dilated	Dilated
C-24	♂	10	20	Dilated	Dilated	Dilated
C-25	♂	9	23	Dilated	Dilated	Not dilated
C-26	♂	10	23	Dilated	Dilated	Dilated

mals a cuboidal epithelium lined the intrahepatic biliary ducts and a high columnar epithelium the mucosa of the gallbladder. Fifteen days following the removal of the gallbladder, in the intrahepatic biliary ducts, "the surface of the epithelium was irregular; new cells projected into the lumen," and "there was apparent bud formation." From forty to seventy-seven days following cholecystectomy, "numerous mucous folds and villi of varying sizes were seen projecting into the lumen of the ducts," and a "change of the epithelial cells from the cuboidal type, with no real resemblance to the gallbladder cells, to high columnar cells" which "approached the morphologic appearance of the epithelial cells of the gallbladder" occurred.

Our investigations were concerned with the morphologic appearance, gross and microscopic, of the biliary system of the dog subsequent to surgical removal of the gallbladder.

Fig. 1.—The extrahepatic biliary ducts of a dog (C-5) ten weeks following cholecystectomy. No gross or microscopic evidence of dilatation of the ducts was noted.

Fig. 2.—Marked dilatation of the extrahepatic biliary ducts of a dog (C-6) ten weeks following cholecystectomy. Although the extrahepatic biliary ducts were markedly dilated grossly and also microscopically, no pertinent changes were noted in the intrahepatic ducts and in the parenchyma of the liver (see fig. 3).

METHOD

From twenty-four apparently healthy dogs, weighing between 7 and 17 Kg., the gallbladders were removed by dividing the cystic duct as close to the ductus choledochus as was practicable. Subsequently the gallbladders were examined grossly and microscopically. The condition of the liver and the extrahepatic biliary ducts was noted at the time of removal of the gallbladder. From one to twenty-three weeks following the cholecystectomy a second laparotomy was performed, and the gross appearance of the liver and the extrahepatic biliary ducts again noted; then the entire system was removed and fixed *in toto*. Subsequently, the whole of the extrahepatic biliary ducts was divided into blocks of from 1 to 2 cm. in length and embedded in celloidin. In each case, sections were prepared from

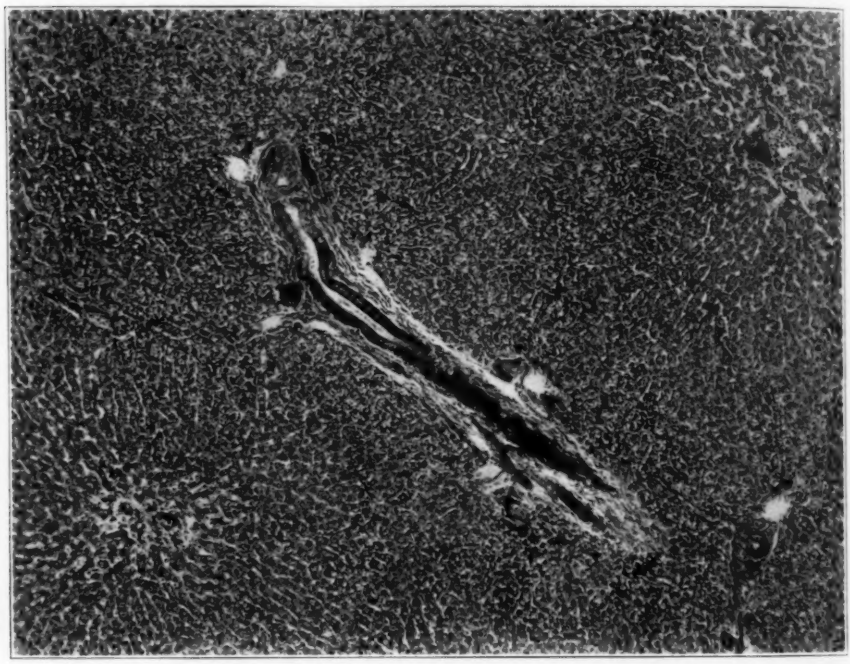

Fig. 3.—Section of the liver of a dog (C-6) ten weeks following cholecystectomy; × 85. Although the extrahepatic biliary ducts show marked dilatation (see fig. 2), gross and microscopic, no pertinent changes are noted in the parenchyma of the liver. A medium-sized intrahepatic duct seen in longitudinal section is not dilated; its lumen is lined with tall columnar epithelium; there are no signs of budding or epithelial proliferation.

every block and from portions of various parts of the liver and stained with hematoxylin-eosin and iron-hematoxylin and by the method of van Gieson.

MORPHOLOGIC OBSERVATIONS

In all of the twenty-four dogs used in these experiments, the biliary system appeared normal grossly at the time of the cholecystectomy and the gallbladders removed showed no gross or microscopic changes.

First Group.—In this group of eleven dogs, the biliary systems were removed between the first and sixth week following the cholecystectomy (table). The extrahepatic biliary ducts appeared grossly distended at the close of the experiment in four of the eleven dogs. Microscopically, however, in only three were the folds of the mucosa low or missing and the lining epithelium flattened in places. In none of the remaining eight dogs was there any microscopic evidence of undue dilatation of the ducts, for in all the mucosa was thrown into folds and lined by a

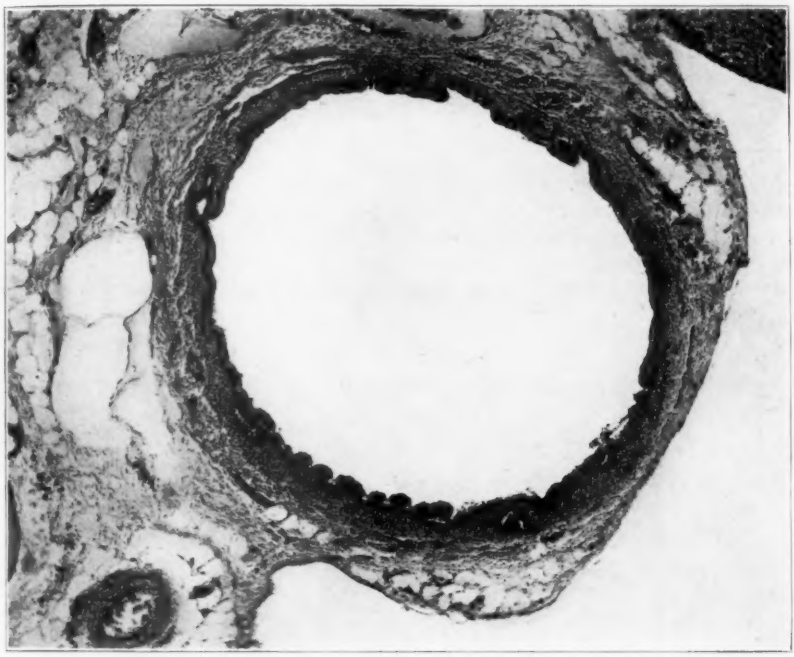

Fig. 4.—Section of a small hepatic duct at the porta hepatis of a dog (C-26) twenty-three weeks following cholecystectomy; × 45. The tall columnar epithelium lining the lumen is flattened, the folds of the mucosa are few and low, and the indentations are shallow.

single row of tall columnar epithelium. No pertinent changes were noted in the parenchyma of the liver or in the intrahepatic biliary ducts.

Second Group.—In this group of seven dogs, the biliary systems were removed between the eighth and twelfth week following the cholecystectomy (table). The extrahepatic biliary ducts appeared grossly distended at the close of the experiment in four of the seven dogs, only one of which, however, exhibited microscopic evidence of a dilatation such as lowering or absence of the folds of the mucosa and occa-

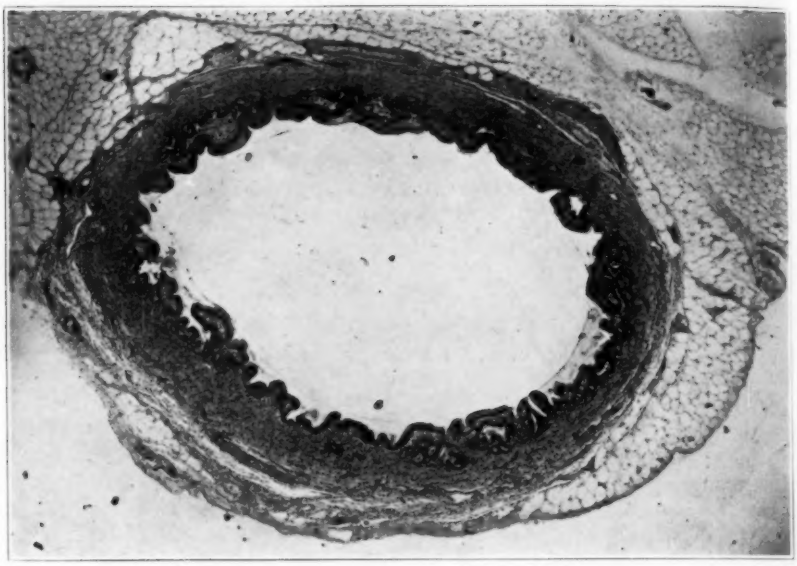

Fig. 5.—Cross-section of the ductus choledochus of a dog (C-7) from near the junction of the cystic and hepatic ducts two weeks following cholecystectomy; × 25. There is no evidence of dilatation of the duct: The lumen is well shaped and lined with a single row of tall columnar epithelium; folds project into the lumen; indentations of the mucosa are frequent. Epithelial-lined lumina in the wall are numerous.

Fig. 6.—Cross-section of the ductus choledochus of a dog (C-8) two weeks following cholecystectomy; × 25. There is marked dilatation of the ductus choledochus: The lining epithelium is flattened in places; the folds of the mucosa are low or absent; the indentations are shallow. Epithelial-lined lumina in the wall are frequent.

sional flattening of the lining epithelium. No changes were noted in the parenchyma of the liver or in the intrahepatic biliary ducts (figs. 1 to 3).

Third Group.—In this group of six dogs, the biliary systems were removed between the sixteenth and twenty-third week following cholecystectomy. In all but one of these animals the extrahepatic biliary ducts appeared grossly distended at the close of the experiment and exhibited some microscopic evidence of dilatation. The parenchyma of the liver and the intrahepatic biliary ducts disclosed no pertinent microscopic changes.

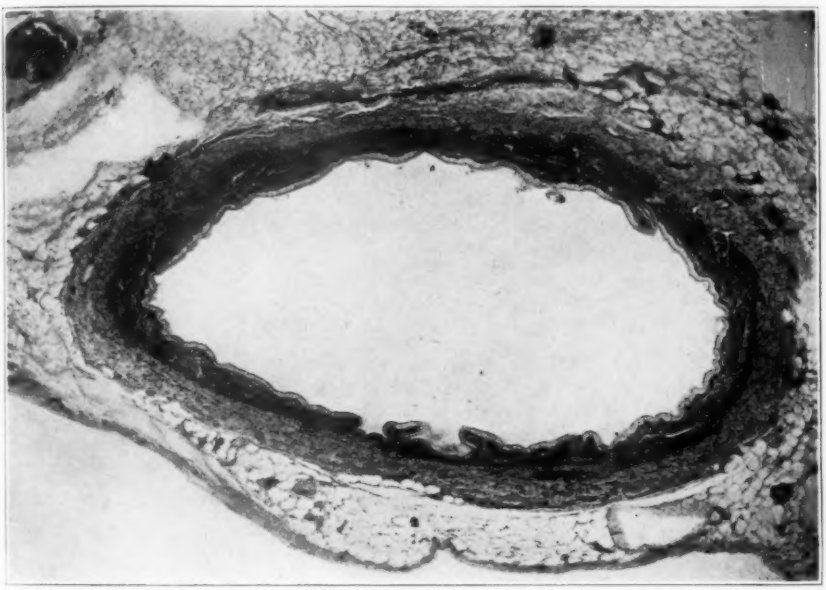

Fig. 7.—Cross-section of the ductus choledochus of a dog (C-25) just proximal to its intramural portion twenty-three weeks following cholecystectomy; × 25. The absence of muscle fibers in the wall of the ductus choledochus is conspicuous. The folds of the mucosa are few, the indentations shallow. Numerous epithelial-lined lumina are seen in the mucosa, but no glands. The lining epithelium is tall, columnar and slightly flattened in places.

It should be restated that in none of the twenty-four dogs were there any pertinent changes in the parenchyma of the liver or gross or microscopic evidence of a dilatation of the intrahepatic biliary ducts following cholecystectomy (fig. 3). The lumina of the small and middle-sized biliary ducts were open and lined by a single row of low columnar epithelium. While the mucosa of these ducts was void of folds, the large intrahepatic ducts showed slight elevations and shallow indentations of the mucosa.

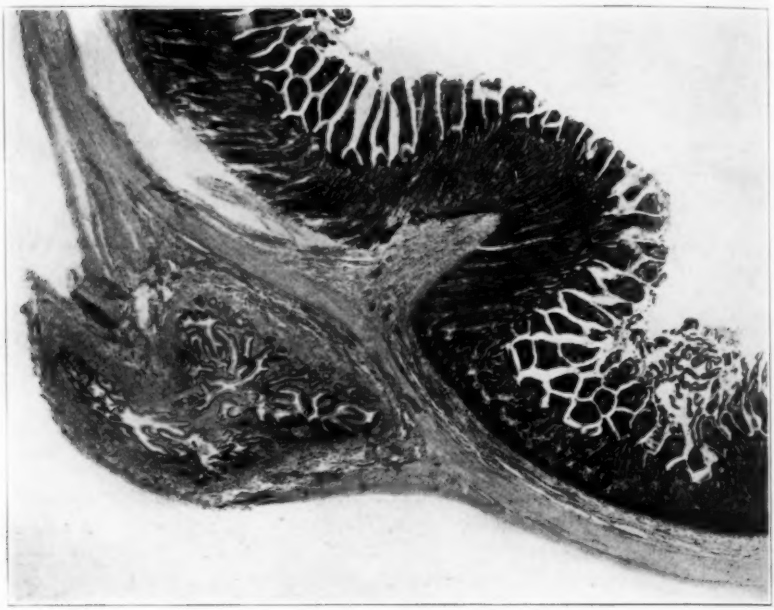

Fig. 8.—Cross-section of the intramural portion of the ductus choledochus of a dog (C-26) twenty-three weeks following cholecystectomy; × 14. The longitudinal layer of the muscular coat of the duodenum is seen to be split in order to admit the ductus choledochus. No muscle fibers are seen in the wall of the duct opposite the duodenum.

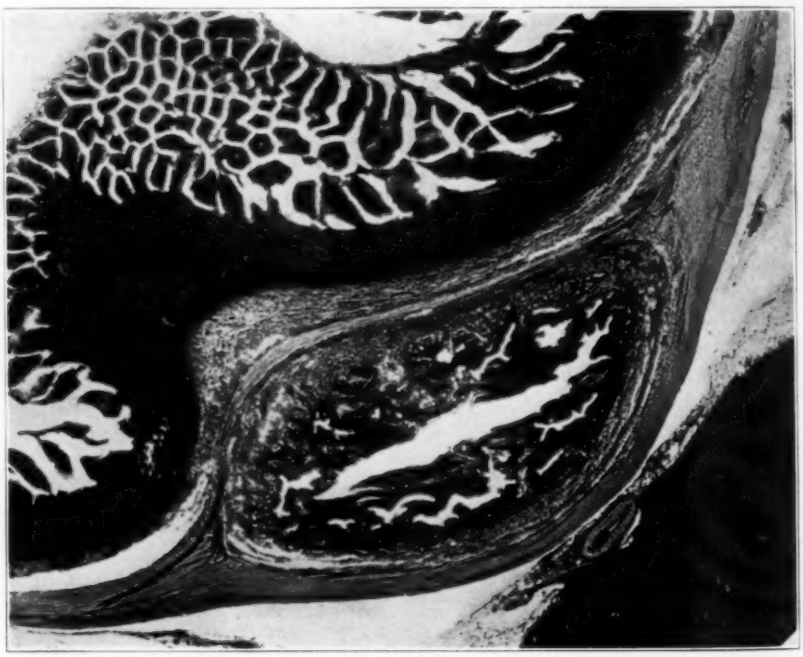

Fig. 9.—Terminal end of the ductus choledochus of a dog (C-25) twenty-three weeks following cholecystectomy; × 14. The duct is seen passing through the circular layer of the muscular coat of the duodenum. The isolated muscle bundles scattered about the external layer of the wall of the ductus choledochus appear to be part of the circular layer of the duodenal wall, the muscle bundles of which have separated and changed their course in order to admit the duct.

Of the extrahepatic biliary ducts, particular attention was paid to the cystic stump, of which sections were obtained in twenty of the twenty-four dogs. In only four of these was there any definite evidence of dilatation (table). Such changes were always associated with dilatation of the rest of the extrahepatic biliary ducts and did not occur without such.

In all the extrahepatic biliary ducts there were frequent outpouchings of the mucosa toward the external layers (fig. 5). Occasionally some of these outpouchings appeared as round or oblong lumina lined by a single row of low columnar epithelium the cells of which had a

Fig. 10.—Section through the papilla of Vater of a dog (C-7) two weeks following cholecystectomy; × 14. The lumen of the ductus choledochus is seen to merge with the lumen of the duodenum. The muscle fibers in the wall of the duct are scanty and irregularly distributed.

lightly staining cytoplasm and a flat nucleus; apparently they were mucous glands. The number of the epithelial-lined lumina in the wall of the ducts varied considerably in different dogs and in various parts of the tract of the same dog. No increase in size or number of these outpouchings or of the folds was noted in the series examined, nor was there any evidence of budding of the folds or proliferation of the surface epithelium. External to the thin tunica propria mucosae the wall of the medium-sized and large intrahepatic and also the extra-

hepatic biliary ducts was seen to be composed of a dense layer of connective tissue rich in fibers arranged more or less circularly.

The wall of all the biliary ducts was noted to be void of muscle fibers (figs. 4 to 7). In the wall of the terminal portion of the ductus choledochus scattered bundles of muscle fibers were noted occasionally, but not until the duct had actually reached the duodenum (figs. 8 to 10). The course and arrangement of the muscle bundles in sections across the intramural portion of the ductus choledochus left some doubt as to the existence of an anatomic sphincter of Oddi in the dog.

COMMENT

The effects of the cholecystectomy, it seems, must primarily depend on the preoperative working condition of the biliary system and also on individual anatomic variations regarding the arrangement of the ducts. For this reason we eliminated from our series dogs the livers of which appeared grossly damaged or the gallbladders of which were not grossly and microscopically normal. At present too little is known of the anatomic variations in the arrangement of the biliary ducts to be of use in interpreting the effects of surgical removal of the gallbladder of the dog. While it seems logical to attribute a great deal of importance to the mechanism regulating the flow of bile into the duodenum, it must be admitted that no exact knowledge is at hand about this function.[12] Our morphologic observations on the intramural portion of the ductus choledochus, which will be presented in detail elsewhere, leave us in serious doubt as to the existence of an anatomic sphincter of Oddi in the dog. This again helps to confuse rather than to explain the situation.

In a preliminary report we presented data on twelve dogs the biliary systems of which were studied morphologically from two to sixteen weeks after cholecystectomy.[13] The results obtained in this group of animals seemed to warrant the conclusion that "dilatation of the extrahepatic biliary ducts, if it occurs, is independent of the time elapsing after removal of the gallbladder." However, the present final report on twenty-four dogs the biliary systems of which were studied from one to twenty-three weeks following cholecystectomy does not support this contention. Of eighteen dogs studied between the first and twelfth weeks following cholecystectomy, only four (22.2 per cent) showed microscopic evidence of a dilatation, while identical changes were noted in five of six dogs (83.3 per cent) the biliary systems of which were

12. Halpert, Béla: The Gallbladder: Its Functions and Some of Their Disturbances in the Light of Recent Investigations, Arch. Surg. **19**:1037 (Dec.) 1929.

13. Healey, Claire; Rewbridge, A. G., and Halpert, Béla: Effects of Cholecystectomy on the Biliary System, Arch. Path. **9**:1295 (June) 1930.

studied between the sixteenth and twenty-third weeks after cholecystectomy. Our present final studies thus indicate that the extrahepatic biliary ducts may dilate at any time subsequent to cholecystectomy and that microscopic evidence of dilatation develops about four times more frequently between the fourth and sixth months than in the first twelve weeks after removal of the gallbladder.

SUMMARY AND CONCLUSIONS

The gallbladders of twenty-four apparently healthy dogs were removed and with the rest of the biliary systems were studied morphologically from one to twenty-three weeks following cholecystectomy. The results obtained suggest the following: (*a*) The parenchyma of the liver and the intrahepatic biliary ducts suffer no pertinent changes in the first six months following surgical removal of the normal gallbladder. (*b*) The extrahepatic biliary ducts may dilate at any time subsequent to cholecystectomy; microscopic evidence of dilatation develops about four times more frequently between the fourth and sixth months than in the first twelve weeks following removal of the gallbladder.

The variable effects of cholecystectomy on the extrahepatic biliary ducts may be dependent on the preoperative working condition of the biliary system, on individual anatomic variations of the structure and the arrangement of the ducts and, finally, on the mechanism regulating the flow of bile into the duodenum.

A study of the intramural portion of the ductus choledochus, in the present series of animals, casts serious doubt as to the existence of an anatomic sphincter of Oddi in the dog.

LYMPH VESSELS IN RABBIT CARCINOMA

WITH A NOTE ON THE NORMAL LYMPH VESSEL STRUCTURE OF THE TESTIS

FERDINAND C. LEE, M.D.

AND

R. CARMICHAEL TILGHMAN, M.D.

BALTIMORE

In 1908, Evans [1] published a short article on the occurrence of newly formed lymphatic vessels in malignant growths. In this paper he stated that important publications and books of reference, such as those of Borst,[2] Ribbert, Ziegler, Lubarsch-Ostertag and Thoma, failed to report "any instance in which proper lymphatic vessels were found growing in malignant tissue." In fact, that statement holds good today, because examination of more recently published volumes, such as the exhaustive work of Ewing [3] on neoplastic diseases, and of the textbooks of Aschoff,[4] Karsner,[5] Sternberg [6] and Adami,[7] has showed that they have nothing to add to the previous works on this subject. The textbook of MacCallum,[8] however, is an exception, because here it is stated that as a result of the injection experiments of Evans, it is known that lymphatics are abundantly present in human tumors. This work of Evans will be discussed later. Another exception is the textbook of McFarland,[9] in which it is stated that "lymphatics of neoplasms are

From the Surgical Hunterian Laboratory of the Johns Hopkins Medical School. Aided by the Garvan Cancer Research Fund.

1. Evans, H. M.: On the Occurrence of Newly-Formed Lymphatic Vessels in Malignant Growths, with a Demonstration of Their Origin and Ingrowth in the Metastases of a Round Cell Sarcoma, Bull. Johns Hopkins Hosp. **19**:232, 1908.
2. Borst, Max: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902.
3. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928.
4. Aschoff, L.: Pathologische Anatomie, Jena, G. Fischer, 1919.
5. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1929.
6. Sternberg, C.: Lehrbuch der allgemeinen Pathologie und der pathologischen Anatomie, begründet von H. Ribbert, Leipzig, F. C. W. Vogel, 1928.
7. Adami, J. G.: The Principles of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1910.
8. MacCallum, W. G.: A Text-Book of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928.
9. McFarland, J.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1904.

usually plentiful, often superabundant, and may be plexiform or cavernous." This unsupported statement stands, therefore, in marked contrast to the conclusions of other writers on this subject. For the present it will suffice to say that in the course of some work [10] on the vital staining of rabbit carcinoma, the occasion presented itself to study the relationship between the lymph vessels of the normal testis and of the carcinoma which had been transplanted into the testicle.

MATERIAL AND METHODS

Ten rabbits that had been inoculated intratesticularly with cancer were used for the injections. All the animals were about 6 months old. It was soon found, from preliminary injections into other animals with cancer, that injections could be made into the lymphatics on the surface of the testis at almost any time, but that the process became more difficult with the increased age of the growth. Apparently, as the transverse diameter of the testis increased, the peritoneal covering, which forms the visceral layer of the tunica vaginalis propria, also enlarged and kept pace with the tumor growth with the one important difference, as far as the lymphatics were concerned, that the tunica vaginalis was thinner and its lymph vessels were fewer, smaller and it was more difficult to make injections into them. The best specimens were obtained from those that had a tumor growth varying from 13 to 24 days of age. In four of the animals the lymph drainage was obstructed for three hours before the injections were made in order to distend the lymphatic system and thus obtain a more complete injection. The idea of distending lymph vessels to facilitate their injection has been of service in filling the lymph vessels of the liver (Lee [11]), gallbladder (Winkenwerder [12]), and thyroid (Rienhoff [13]). It happened, however, that one of the best injections of the parenchymatous lymphatics (figs. 4 to 6) was one in which the lymph vessels had not been previously obstructed.

India ink or a saturated solution of berlin blue was used for injection. By means of an ordinary syringe equipped with a 27 gage needle these substances were readily injected into the lymph vessels in the tunica vaginalis by direct puncture. This method was not only simple but also accurate, because to any one familiar with the injection of lymphatics there was no possible confusion of the lymph vessel pattern

10. Tilghman, R. C., and Lee, F. C.: The Vital Staining of Rabbit Carcinoma, Bull. Johns Hopkins Hosp. **49**:360, 1931.

11. Lee, F. C.: On the Lymph Vessels of the Liver, Contrib. Embryol. **15**:63, 1923.

12. Winkenwerder, W. L.: A Study of the Lymphatics of the Gall-Bladder of the Cat, Bull. Johns Hopkins Hosp. **41**:226, 1927.

13. Rienhoff, W. F., Jr.: The Lymphatic Vessels of the Thyroid Gland in the Dog and in Man, Arch. Surg. **23**:483 (Nov.) 1931

with that of any other vascular system. The entire superficial lymphatic plexus would immediately fill and drain along large lymph vessels in the mesorchium. These vessels were at once recognized by the presence of numerous valves along their course. In five of the animals injections were also made into the blood vessels in order to check the effect of injection into the lymph system, but the lymph vessel pattern was so definite that in one half of the animals the vascular injection was omitted in order to make the study of the lymph system less complicated. All the material was fixed in solution of formaldehyde. Some of the tissue was cleared in methylsalicylate, while other portions were sectioned as a routine procedure and stained with hematoxylin and eosin.

Fig. 1.—For orientation. Testis of a rabbit with extensive cancer growth twenty days after inoculation. India ink was injected into the lymphatics on the surface at one area, but they did not extend into the small white cancer mass situated in the middle of the area into which injection was made. This small cancer nodule is enlarged in figure 2. Natural size.

From all the material thus obtained three specimens were chosen to illustrate the relationship between the cancer growth and the lymph vessels.

One of these specimens was derived from a rabbit each testis of which had been inoculated with a suspension of rabbit carcinoma in salt solution. Twenty days later the animal showed marked loss of weight, was dragging its left leg, and apparently would not have survived many days. It was killed with ether, and in the abdominal cavity was found the left testis, measuring 5 cm. long and 2 cm. in diameter, obviously the seat of a large cancer growth. The testis was irregular in shape, nodular, and had on its surface a small cancer nodule about 4 mm. in

diameter, which seemed to be loosely attached to the body of the testis (fig. 1). Obviously this nodule was an isolated bit of cancer tissue which probably had been free at one time in the abdominal cavity, had attached itself to the tunica vaginalis propria, and had grown independently of the bulk of the cancer tissue in the testis proper. Indeed, it was common to see such isolated cancer nodules all over the entire peritoneal cavity, the omentum as a rule being most heavily laden with these cancer deposits, with the parietal peritoneum and diaphragm next in order. It was felt that this specimen would prove ideal for deter-

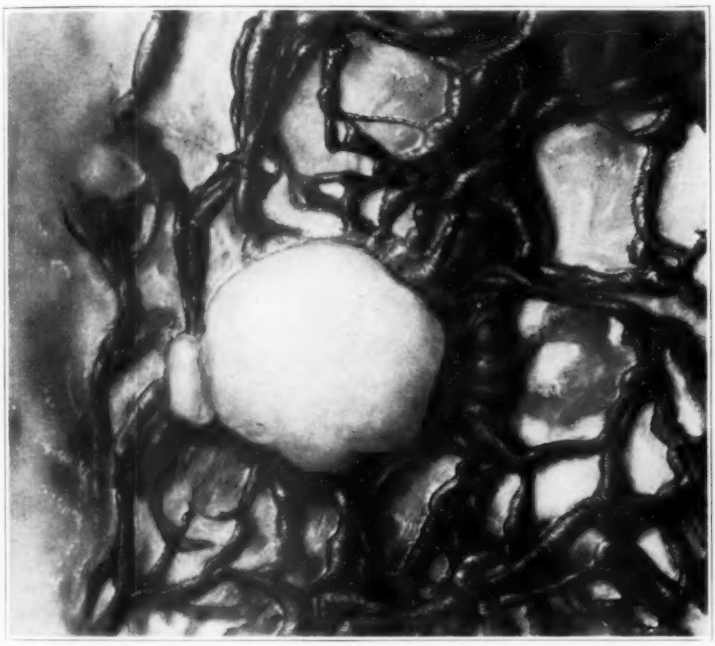

Fig. 2.—Enlarged drawing of nodule shown in figure 1 to show the extensive lymph vessel plexus around the base of the cancer mass, but with no lymph vessels in the cancer nodule itself. The lymph vessels have a superficial and a deep plexus with numerous communicating channels; × 9.

mining what relationship the lymph vessels in the tunica of the testis would have to this little nodule. Accordingly, india ink was injected into the outer layer of the testis, and although the lymph vessels were seen to fill all about the small nodule, not even the smallest vessel on the surface of this little cancer mass was seen to become filled with the injected material.

In figure 2 a magnification of this area is presented, and it can be readily seen that large lymph vessels and sinuses, some of which are in a deeper layer, come to the base of the cancer nodule but do not

send any branches into it. A curious feature of the entire plexus is the intricate and varied pattern of the vessels which intertwine in an irregular fashion, leaving clear areas, which in turn are surrounded by a mass of large lymph trunks. The vessels themselves also show the typical character of lymph vessels by their frequent branching and sudden changes in caliber. The general pattern of these vessels is no different from that seen on the surface of any testis which has no attached cancer nodule. Obviously the only way of determining what happened to the lymph vessels under the nodule was by histologic section. Serial sections were cut, and it was seen that the lymph vessels

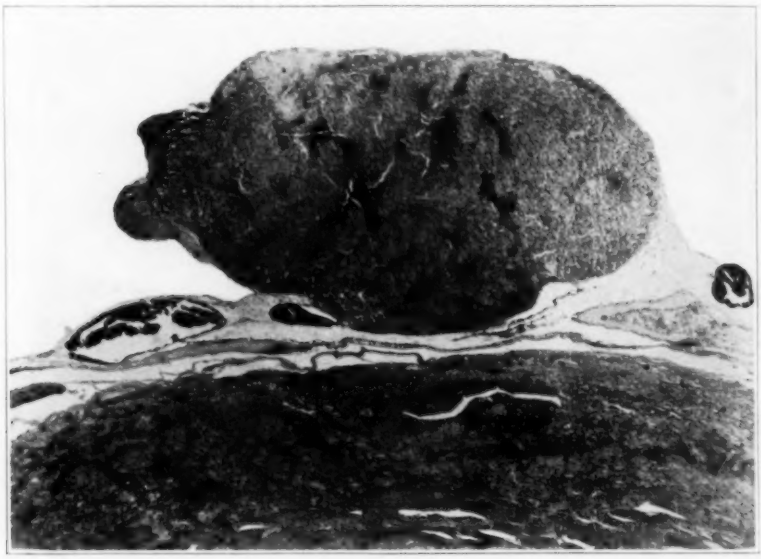

Fig. 3.—Cross-section of the cancer nodule shown in figures 1 and 2. It will be seen that the nodule is not firmly attached to the body of the testis, and that the lymph vessels containing the india ink are in contact with the nodule but do not have any branches that extend into the nodule, indicating that the neoplasm has no lymph channels of its own. The darker areas in the nodule are areas of cell degeneration and pyknosis; × 18.

passed underneath the nodule, even at that point at which the nodule was nearest the main body of the tumor (fig. 3).

Examination of this photograph shows the nodule entirely devoid of lymph vessels except at its attachment, where the vessels are not only few in number but are also compressed. No lymph trunks enter the testis underneath the nodule. In none of the serial sections was there the slightest evidence of lymph vessels entering the cancer nodule. The dark-staining areas in the cancer nodule and in the testis represent foci of necrosis with condensation of dark-staining nuclei, and should not

be confused with the lymph vessels which photograph still blacker because they contain india ink. The scant blood supply to this mass was derived from a few small vessels which passed through the delicate areolar tissue connecting the nodule to the testis. The small tumor mass was quite compact, in spite of the numerous areas of necrosis; no loose areolar tissue surrounded the blood vessels. It is, of course, impossible to predict whether this nodule would have eventually joined the main carcinomatous mass of the testis, but that an amalgamation would have been established seems reasonable from a consideration of the second specimen.

The second specimen was obtained from a rabbit that had been inoculated with cancer thirteen days previously. The animal contracted an acute respiratory infection and died suddenly; the body was still warm when the abdomen was opened. Both testes showed large cancer growths, and the left one also had a small white nodule on its free surface similar to the one just described. In this second case, however, the nodule was flat, and seemed more firmly attached to the testis than in the first case; it was also smaller. Injections of india ink were also made into the lymph vessels in the tunica vaginalis, and it was found that a large and elaborate lymphatic plexus was filled around the base of the nodule, but that no vessels were seen on the surface of the small tumor mass. In all essential points the lymph vessel pattern was the same about the base of the two specimens. Serial sections showed that although a broad base joined the tumor nodule to the testis, nevertheless the area through which cancer tissue was continuous from testis to nodule was relatively small. In fact, the fibrous tissue of the tunica almost formed a completely separating membrane between the cancer tissue of the nodule and of the testis. Again, as in the first specimen, none of the mass injected was found in any part of the cancer nodule, indicating that there was no continuity of the lymph vessels in the tunica vaginalis of the testis with any structure or spaces in the cancer nodule.

Thus far all the observations indicated that there were no lymph vessels in the rabbit carcinoma proper. Accordingly, it was necessary to determine how the lymph vessels which were in the normal testis disappeared. Examination of the serial sections from the two specimens described showed that the cancer cells invaded the lymph vessels, proliferated inside of the lumen of these vessels, eventually filled the lumen, and finally, by fusing with the extravascular cancer, completely destroyed the walls, and with them the last vestige of the lymph vascular system.

Further evidence confirming the observations just described regarding the absence of lymph vessels in rabbit carcinoma was furnished by

fortunate injection into the superficial lymph plexus of the right testis of a rabbit that had been inoculated twenty-three days previously with cancer. Growth of the cancer, however, was not equal in the two testicles, for when the animal was killed, the right testis measured only 45 mm. long and 7.5 mm. in diameter, whereas the left one was 55 mm. long with a diameter of 15 mm. In brief, the right testis was small, with only a moderate cancer growth in the glandular tissue, whereas the left one was more than four times as large. Injection into the superficial lymph vessels of the left testis did not show any penetration into the testis proper, but when the surface lymphatics of the right testis were filled, it was seen that some of the india ink went deeper into the body of the gland. A cross-section of the gland showed that the cancer

Fig. 4.—Sketch of a cleared thin section of a cancer-bearing rabbit testicle showing the lymph vessels of the normal tissue filled with india ink and the cancer areas devoid of the injection. The collecting lymph vesseis empty into the large trunks of the mediastinum testis. The proliferating cancer cells are obliterating the lymph vessel in their growth as is seen in the lower portion of the illustrations. A curious feature is the condensation of lymph vessels around one nodule. The marked area is shown at higher magnification in figure 5; × 12.

occupied the central portion of it, and that the peripheral zone only had received the india ink, indicating that normal testicular tissue was still present near the tunica vaginalis. A thin longitudinal section of the testis cleared in methylsalicylate showed that the lymphatics in the body of the testis formed an elaborate network of vessels which were plexiform, with only small differences in caliber, without any large collecting trunks in the gland itself, but emptying into the large vessels on the surface (fig. 4). Inspection of this illustration shows several areas

entirely devoid of any injected mass, indicating the presence of cancer, with the adjacent normal tissue having a rich plexus of lymph vessels.

The actual structure of the lymphatics can be appreciated better from a study of figure 5, which is an enlargement of the area marked out in figure 4. It will be seen that the vessels form an extensive and elaborate plexus consisting of small vessels with numerous irregular dilatations or sacculations which never exceed a certain size, and which are frequently found parallel to one another. The vessels outline a central area into which they project their sharply pointed processes for a short distance. This central area was demonstrated by histologic section to be solid cancer tissue. In a like manner the other clear area

Fig. 5.—Enlarged drawing of area marked out in figure 4. The lymph vessels filled with ink partly surround the cancer growth, which is devoid of these vessels and is represented by the clear area. It will be noted how relatively small the vessels are at the periphery of the cancer, indicating their compression and obliteration by the neoplasm. The numerous enlargements and constrictions of the vessels are typical of a lymphatic pattern; × 30.

immediately above it in figure 4 was also cancer. But the intervening tissue containing a large number of lymph vessels was predominantly normal testis.

Figure 6, taken from the upper central portion of figure 5, shows a section of several seminiferous tubules partly surrounded by cancer cells and having numerous large lymph vessels partly filled with the injected india ink occupying most of the space between them. In the upper portion of the illustration the cancer tissue is relatively less, the tubules

are more distinct and the lymph vessels are correspondingly large. In the lower part of the figure, however, the tubules are not only compressed but even invaded by the cancer. The lymphatics in their turn are also closed down to a small lumen because of the tumor growth, and it is obvious that the lymph vessels here would have been completely destroyed within a short time. When examined under higher magnification the endothelial cells of the lymphatics can be readily identified.

Some of the steps in this process of invasion deserve a more detailed description because the usual sources of such information are from clinical material in which injections into the lymph vessels have not been made and therefore a confusion might arise as to whether the cancer cells were invading a lymph vessel or a vein. Besides, even such good clinical material as is pictured in Handley's [14] book on the breast does not present such a connected story as can be gleaned from a study of tissue which is, first of all, being invaded by cancer, and, in the second place, has had injections made into its lymph vessels so that they can be easily identified.

It seems that the proliferating cancer cells do not invade a lymph vessel directly, but first attempt to grow around it, and then compress it. During this strangulation process the wall of the lymph vessel is destroyed at one or more points, and the cancer cells thus gain access to the lumen. Once inside the vessel, the malignant growth proliferates along the lines of least resistance. If there is still some lumen left at the point of penetration, the cancer cells will extend out as one mass to fill up the lumen, before they will progress along the inside of the wall to any extent.

Growth of the cancer cells within the lumen extends simultaneously in two directions. Should the lumen at the point of entry be large, the cancer cells will proliferate locally, forming whorls of greater or less size but leaving the vessel wall relatively untouched. India ink was frequently seen within the layers of such whorls, indicating not only the spiral arrangement of the neoplasm, but also its loosely knit character. Should the lymph vessel be invaded at several places about the same time, then the spread of the cancer will be toward the center of the vessel without the production of whorls, unless the vessel has an unusually large diameter. In such an instance the india ink was found as a thin streak in the middle of the vessel.

The other direction in which cancer spreads is directly down the center of the lymph vessel. The proliferating mass resembles much a finger as it is inserted into a glove, except that the cancer mass does not have a tendency to touch the vessel wall, but grows forward for a

14. Handley, W. S.: Cancer of the Breast and Its Operative Treatment, ed. 2, London, A. Murray, 1922.

comparatively long distance. The advancing growth has a relatively blunt tip with its cells having slightly more cytoplasm than ordinarily, and with nuclei situated more in the periphery of the cell body. This central, onward growth is arrested when it meets an object, such as another cancer mass which has appeared independently along the course of the lymph vessel under consideration. At other times the tip becomes attached to the sides of the lymph vessel near a division of the vessel or near a valve. It is remarkable how a thin and delicate valve leaflet can temporarily impede the progress of the growth and guide it toward the

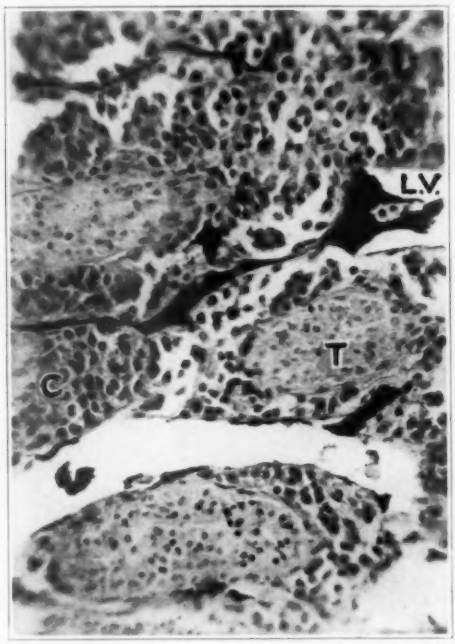

Fig. 6.—Photograph of a histologic section taken vertically at the top center of figure 4 to show how the cancer growth, *C*, is compressing not only the lymph vessels, *L.V.*, filled with india ink, but also the seminiferous tubules, *T*. Note the invasion by the cancer of the lymph vessel at the point, *L.V.*, and the delicate endothelial lining of the lymph vessels; × 130.

center of the stream. Figure 7 shows a relatively large lymphatic containing india ink, with a cancer mass which has impinged on the leaflet, *V*, and has grown along the leaflet without penetrating it. This instance shows well how the cancer growth follows the lines of least resistance.

The preparations which have been described in the preceding paragraphs also serve to convey an idea of the normal distribution of the lymph vessels of the testis. It is true that the lymph vessels of the testis have been described in detail before, the best account probably

being that of Gerster,[15] whose work was substantiated by Regaud.[16] Gerster, however, found it difficult to make injections into the lymph vessels in the testis of rabbits and stated that he could fill only those in the albuginea; he was unable to visualize the lymph vessels in the body of the testis except from histologic preparations stained with osmic acid. All his specimens for injection were obtained from rams and from man. His illustrations show a close resemblance in general pattern to those just described for the rabbit.

The illustrations in figures 1 to 3 thus also serve to give an idea of the normal lymphatic distribution on the surface of the rabbit testis. It

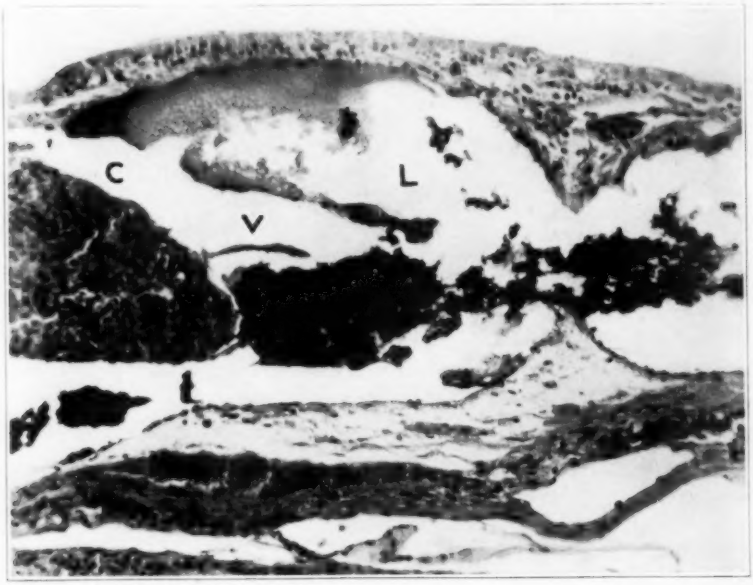

Fig. 7.—Photograph of a histologic section through the tunica vaginalis of a rabbit's testis, showing a lymph vessel, *L*, into which india ink was injected, being invaded by a cancer mass near *C*. It will be noted how the cancer has spread along the valve leaflet, *V*, without penetrating it; × 80.

is true that the testis in every instance was the seat of cancer and therefore not a normal organ; but since the lymph vessels on its surface were not infiltrated by the cancer mass which occupied the body of the testis, it is reasonable to assume that these vessels represented in a measure at least the normal pattern. It must, however, be pointed out that the concentration of lymph vessels about a cancer nodule as is

15. Gerster, R.: Ueber die Lymphgefässe des Hodens, Ztschr. f. Anat. u. Entwcklgsgesch. **2**:36, 1876.

16. Regaud, C.: Les vaisseaux lymphatiques du testicle, Compt. rend. Soc. de biol. **4**:659, 1897.

shown in figure 2, where unusually large vessels have united to form bays about the base of a tumor nodule situated on the surface of the testis, or the similar condensation of lymph vessels about a small cancer mass situated within the body of the gland as is represented by the small circular area in figure 4, cannot be considered normal. But when such areas are disregarded, and only those areas are considered which are free of cancer, then it is reasonable to believe that the lymph vessels in these last named places represented the normal pattern.

Examination of figure 4 shows numerous large lymph trunks situated on the posterior aspect of the testis which receive many tributaries that extend into the body of the testis. A higher magnification of the terminal portion of such a plexus, as shown in figure 5, shows a vessel pattern similar to that described in other parenchymatous organs such as the liver (Lee) and thyroid (Rienhoff).

In brief, from the material obtained in the study of the lymph vessels of the cancer-bearing testes of rabbits, some idea of the distribution and arrangement of these vessels in the normal testes of the animals is obtained. It seems that the lymph vessel pattern for the rabbit's testis is similar to that of the testes of other animals. Apparently injections had not previously been made into the parenchymatous lymph vessels of the rabbit's testis.

COMMENT

Probably the earliest account of lymph vessels in human tumors was given by Krause,[17] in 1863, in a short article which seems to have been overlooked by many who have written on the subject since that time. Krause made injections into tumors which were received still warm from the operating room. His method was to choose cancers that had attached themselves to the skin, and then to make injections into the lymph vessels of the skin with syringe and needle. By this method he claimed to have filled lymph vessels in a myxoma (myxosarcoma?) of the vulva, a scirrhous carcinoma of the breast, two cases of medullary carcinoma of the breast, and a recurrent medullary carcinoma of the hip. His illustrations, taken from the first and last cases, show vessels which certainly resemble lymph vessels. It must be pointed out, however, that no convincing evidence is presented that the lymph vessels were really surrounded by cancer cells. There are no illustrations to show this all-important relationship. Besides, it is quite possible that the vessels into which injections were made were in normal tissue which was about to be invaded by the cancer growth.

An important contribution to the question of whether lymph vessels are present within malignant growths was furnished by Evans in 1908.

17. Krause, W.: Ueber Lymphgefässe in Geschwülsten, Deutsche Klin. **15:** 377, 1863.

He injected india ink into the distended lacteals on the surface of the small intestine from a patient who had died of round cell sarcoma of the neck with metastases, among other regions, to the bowel. The mass injected penetrated the muscular, submucous and mucous coats. Cleared specimens showed an extensive lymphatic plexus within a small tumor mass situated wholly in the mucosa. Microscopic sections of the tumor nodule demonstrated the mass injected to be within endothelial-lined spaces.

This report of Evans is probably the best that can be found in the literature on this subject at the present time. It is remarkable to find that the sarcoma cells did not compress the lymph vessels, but actually promoted their growth. It would have been interesting to have had more sections through the sarcoma nodule in order to see what blood supply was being furnished, because it is reasonable to suppose that wherever blood vessels find their way in soft tissues, they will always be surrounded by some areolar tissue, and it is therefore possible to have lymph vessels accompanying the blood vessels into a tumor. It is furthermore remarkable to note that in his figure 1 several of the small lymph radicles in the tumor actually extend to the outermost portion of the tumor; ordinarily lymph vessels never are found so near to the lumen of the bowel.

It must also be pointed out that Evans has not given a convincing account of the tumor with reference to its lymph vessels in so far as he has made out a clear case for the proposition that the tumor has replaced normal tissue and that the injected lymph vessels are newly formed in the tumor and were not originally situated in the tissue, being only distorted and dislocated by the neoplasm (MacCallum [18]). Furthermore, in his figure 2, the so-called proliferating endothelial cell may possibly be viewed as one that is being compressed by the tumor growth rather than a cell that is working its way into a mass of sarcoma cells.

Besides, there is also the possibility that an inflammatory process might have been part of the mass, particularly in view of the limited description of the cytology of this tumor and its close proximity to the lumen of the bowel. On this basis, following the work of Coffin,[19] it is reasonable to consider some of the lymphatics as being in granulation tissue.

It is possible, however, that a great difference exists between the relationship of lymph vessels in human sarcoma and in the carcinoma of the rabbit. Perhaps the nature of the growth alone is responsible for this variation. The chief points that indicate that there are no lymph vessels within rabbit carcinoma are these: In the first place, the

18. MacCallum, W. G.: Personal communication.

19. Coffin, T. H.: On the Growth of Lymphatics in Granulation Tissue, Bull. Johns Hopkins Hosp. **17**:227, 1906.

specimen described in figures 1 to 3 demonstrates that if lymph vessels were present in the nodule, the only means of pouring their contents into other lymphatics and thus establishing drainage must necessarily have been through the lymphatics on the surface of the testis where the cancer nodule was attached. And even though lymph vessels were demonstrated at the base of the nodule, there were no extensions of these vessels, or communications with these vessels, within the small tumor mass itself. It might be argued that the isolated bit of cancer tissue which later formed the nodule also contained lymphatic endothelium, and that as the nodule grew the lymphatic system increased likewise. But even if this were true, no avenue for the escape of the lymph would have been demonstrated. It seems unlikely that any single vessel, much less any group of vessels, could have avoided the rich plexus of lymph vessels which were outlined in the tunica vaginalis. Furthermore, the cancer nodule was compact, with no spaces which might be taken for lymph vessels, and with the characteristic poor blood supply which was derived from the testis, and along the vessels of which no possible spaces for lymph vessels were seen.

In the second place, the rabbit cancer cells penetrated the lymph vessels and entirely supplanted them. Not only were lymph vessels destroyed, but all normal tissue disappeared, and in its place there developed a mass of cancer cells which extended beyond the ordinary confines of the normal tissue. Now, the only possible way for the cancer growth to get a lymph system would be to have these vessels follow in the wake of the cancer growth, and at all events such lymph vessels must communicate with those on the surface in order to have any drainage at all. But no such lymph vessels were seen in the tumor when injection was made into superficial vessels. There is still a possibility that the proliferating cancer cells in their growth might spare a few vessels and thus leave a skeleton lymph system for the tumor; however, examination of the sections showed conclusively that the cancer cells destroyed all tissue that was in the way of its growth. The only time that lymph vessels were seen about cancer cells was when there was normal tissue at hand, and the lymph vessels were found in this normal tissue.

The most pertinent article on the subject under discussion is by Goldmann, written in 1911. Being interested in the biology of neoplasms, particularly from the point of view of their blood and lymph supply, he made numerous vascular injections of mouse carcinoma transplanted into the peritoneum of animals of this same species. He was able to show conclusively that a tumor mass which had attached itself to the serous surface of the intestine received an extensive blood supply from the bowel, but in no instance were any lymph vessels seen to extend from the bowel wall to the tumor mass. Ink was injected into

the lymph vessels of the bowel with a fine needle and a syringe. Injection was made only into the submucosa because this layer is apparently the only one in the intestinal wall of the mouse that has a lymph plexus. These observations of Goldmann are in absolute agreement with those reported herewith on rabbit carcinoma. One interesting point of difference, however, must be mentioned. In the mouse, the lymphatic plexus nearest the cancer was separated by two layers, the muscular and serous coats, whereas in the rabbit the cancer mass was situated directly on the serous coat into the lymph vessels of which injection was made. Apparently even the greater proximity of lymph vessels and cancer did not facilitate any lymphatic extension into the carcinoma.

SUMMARY AND CONCLUSION

India ink was injected into cancer-bearing testes from ten rabbits in order to determine the relationship between the lymph vessels of the testis and of the cancer mass. In no instance were lymphatics found in the cancer mass. Incidentally, the lymph supply of the normal testis of the rabbit was observed and briefly described. Examination of the literature makes it doubtful whether any true newly formed lymph vessels were ever observed in cancer tissue. In conclusion, it may be stated that transplantable rabbit carcinoma does not have any lymph vessels.

RECONSTRUCTION OF A CONJUNCTIVAL SAC WITH THIERSCH GRAFTS

D. M. GLOVER, M.D.
AND
M. W. JACOBY, M.D.
CLEVELAND

The epithelial inlay graft described by Esser [1] and developed extensively by Gillies [2] has many useful applications in plastic surgery. We applied the method successfully in reconstructing a conjunctival sac which was completely destroyed by a chemical burn.

REPORT OF A CASE

The patient who presented this unusual plastic problem was a man of 37, a plumber, whose previous history was not significant. He was injured on March 13, 1929, when some alkaline drain compound was thrown in his face, and he was admitted to St. Luke's Hospital on that date. Physical examination showed nothing of importance except for superficial second degree burns scattered over the face, neck and upper part of the chest, hyperemia and edema of the tongue and mucous membranes of the mouth, marked chemosis of the right eye, some haziness of the cornea and marked edema of the lids. There was moderate injection of the conjunctivae of the left eye.

The hyperemia of the mouth cleared up in three or four days with frequent irrigations with salt solution, and the superficial skin burns treated with 5 per cent tannic acid jelly were clearing up rapidly when the patient was discharged from the hospital on March 19, six days after his injury. The burn of the right eye, however, was a serious one with involvement of the ciliary body to such an extent that the corneal circulation was impaired, with resulting necrosis of the latter and destruction of the anterior chamber. Enucleation of the eye was advised, but for several weeks the patient refused to have this done. He finally consented and was admitted to the ophthalmologic service on April 18. Enucleation was done under gas-oxygen anesthesia on the following day (Dr. Jacoby), and a glass globe was implanted in the orbit. The conjunctivae were found to be almost completely destroyed, and the eyeball was dissected from a mass of freely bleeding granulations. The patient was again discharged from the hospital on April 25, six days after the enucleation. In spite of the low grade infection present, the sutures in the bulbar fascia held and the glass globe was fortunately retained. Since the conjunctival sac was completely destroyed, the eyelids soon became adherent tightly to the bulbar fascia over the glass globe and to each other.

From the Departments of Surgery and Ophthalmology, St. Luke's Hospital.

1. Esser, J. F.: Plastic Surgery of Face, Ann. Surg. **65**:297 (March) 1917.

2. Gillies, H. D.: Plastic Surgery of the Face, New York, Oxford University Press, 1920.

At this juncture, the condition of the injured orbit was roughly that depicted in figure 1. (Unfortunately no photograph was taken at this time.) The lids were tightly sealed together and depressed in an unsightly manner. It was decided to attempt to reconstruct the conjunctival sac by a modification of the Esser inlay method to enable the patient to wear an artificial eye.

The patient was readmitted to the hospital on June 7 for this operation, which was done the following day under nerve block with procaine hydrochloride (Dr. Glover). First the margins of the lids were dissected free and the underlying scar tissue was removed, undermining the lids nearly to the orbital margin. A mold of sterilized dental composition, softened in hot water, was then fashioned to fit snugly in the pocket formed under the lids (fig. 2). The cavity was then packed with gauze wet with hot salt solution to control the bleeding, while a thin Thiersch graft was cut from the inner aspect of the arm where the skin is thinnest and of finest texture. (We prefer a long, narrow-bladed amputation knife for cutting these grafts. It is absolutely essential that the surface to be grafted be absolutely free from bleeding when the graft is applied.) The graft was then wrapped carefully about the mold, with the cut or deep surface of the graft outside. This mold

Fig. 1.—Appearance of the patient after enucleation. The right conjunctival sac had been completely destroyed by a chemical burn.

covered with the Thiersch graft was then inserted into the pocket prepared for it, and fine dermal, mattress sutures were passed through both margins of the lids, catching the edge of the graft to keep it from slipping (fig. 3). When the sutures were tied, the margins of the lids were approximated. A pressure dressing of gauze and bandage wet with physiologic solution of sodium chloride was applied over the eyelids, it being important that no dead space develop between the graft and its bed during the first twenty-four hours. Oiled silk was bandaged over the moist dressings to minimize evaporation. Warm physiologic solution of sodium chloride was added every four hours. The patient left the hospital on the sixth postoperative day. On the eighth day the sutures were removed, and on the tenth day the mold was allowed to come out and the cavity was flushed to clear it of epithelial débris. It was then apparent that the graft had taken in its entirety with the exception of two small spots, 2 or 3 mm. in diameter. Since these small granulating spots did not epithelize rapidly, on June 21 they were curetted, small grafts applied to them, and the cavity packed tightly with moist gauze. These grafts vascularized readily, completing the epithelization of the pocket. The patient continued to wear the mold in the newly formed cavity, in the attempt to keep it from contracting. But, as is well known, Thiersch grafts have the unfortunate habit of contracting for some weeks following their application, and here the contraction

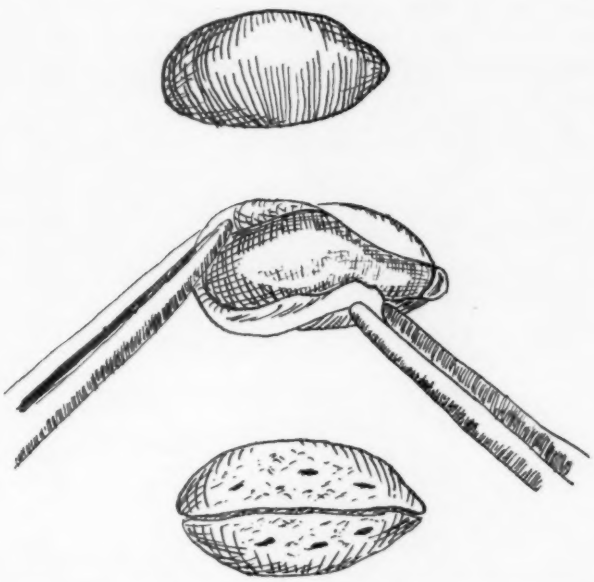

Fig. 2.—The nutmeg-shaped mold of dental composition is made to fit the pocket dissected beneath the eyelids, as shown at the top. The middle and lower sketches show the manner in which the Thiersch graft is wrapped about the mold. The graft has been perforated to prevent accumulation of serum beneath it.

Fig. 3.—The mold with thin graft wrapped about it is now in the pocket and sutures are placed through the margins of the lids, catching the edges of the graft. The dotted lines indicate the extent to which the eyelids are undermined.

of the grafts and spasm of the orbicularis oculi soon forced the mold out, and a small artificial eye (or shell) was substituted. After two or three weeks more this also was forced out by the contraction of the cavity.

We were then faced with the necessity of greatly enlarging the skin-grafted pocket which had become too small to retain any solid object within it. Accordingly, another inlay graft was done under local anesthesia, on August 30, five and one-half months after injury. At this time we did an external canthotomy to serve the double purpose of giving more room and to stop the contraction of the orbicularis oculi temporarily, since we felt the latter factor had caused part of our previous difficulty. Incisions were then made in the skin-lined pocket parallel to the margins of the lids, and the lids were widely undermined again (fig. 4 *A*). A

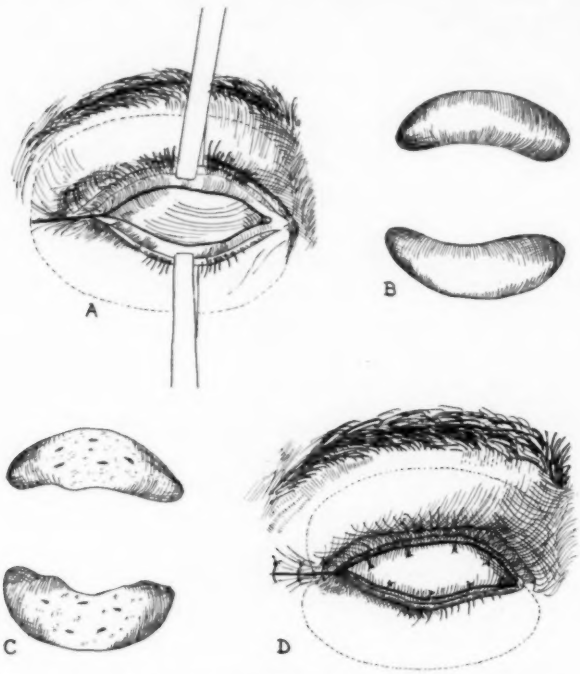

Fig. 4.—The second Esser inlay graft. *A*, heavy lines mark the incisions for the external canthotomy and undermining the lids, and the dotted lines show the extent to which the eyelids were undermined. *B*, a mold or stent is made to fit under each eyelid. *C*, Thiersch grafts are wrapped about each mold. *D*, the molds covered with thin grafts are sutured in place.

dental composition mold was then made to fit the pocket under each lid (fig. 4 *B*). Thiersch grafts were cut and wrapped about these molds or "stents" [3] (fig. 4 *C*) which were introduced into the pockets in the upper and lower lids, and the skin approximated over them with fine dermal sutures (fig. 4 *D*). Moist salt solution compresses were then applied as before, and the patient was allowed to go home. At the end of seven days the sutures were removed and the molds were allowed to

3. These molds are called "stents" by Gillies, after Stent who introduced dental composition.

Fig. 5.—The large skin-lined pocket resulting from the Esser inlay grafts.

Fig. 6.—Appearance of the patient with artificial eye in place three years after injury.

Fig. 7.—Appearance of the skin-lined conjunctival sac three years after injury.

come out, forming a larger skin-lined pocket, with room to spare (fig. 5). A large mold that would completely fill the cavity was made and kept in place for two months, until it was felt that all the contraction reasonably to be expected had taken place. At the end of this time the cavity was a little too large to hold an artificial eye well, and a canthoplasty was done (Dr. Jacoby) to narrow it.

The patient wore a large shell for several months, but for two years or more he has worn the eye that is shown in the photograph taken on March 30, 1932 (fig. 6). The skin-lined conjunctival sac was in excellent condition at this time, three years after injury, and no further contraction or ulceration had taken place. It was gratifying to see how well the skin had adapted itself to its new location, because we were rather apprehensive lest it should contract more or ulcerate from the constant pressure of the artificial eye. It does not seem likely that this will occur later, since the grafted skin has had adequate time to become stabilized (fig. 7).

In retrospect, we believe a large disk-shaped mold could have been used with greater satisfaction at the time of the first inlay graft in place of the nutmeg-shaped mold we used, and perhaps a second stage operation would have been avoided.

Miss Jane Van Gordon made the pen and ink sketches.

PERICARDITIS SIMULATING AN ACUTE CONDITION OF THE ABDOMEN

JOSEPH GREENGARD, M.D.
AND
SAMUEL J. HOFFMAN, M.D.
CHICAGO

During the past few years, three patients have been admitted to the surgical service at Cook County Hospital with a diagnosis of acute appendicitis. All three underwent appendectomies, and in each instance the appendix was grossly and microscopically normal. Subsequent to laparotomy, a definite pericardial friction rub developed, and a diagnosis of rheumatic pericarditis was made.

The incidence of acute abdominal pain at the onset of rheumatic fever, particularly with acute pericardial involvement, is seen not uncommonly. The mechanism of its production is obscure, and its clinical recognition difficult. Geissinger [1] recorded a case in a boy 5 years of age who had a sudden onset of abdominal pain with fever and vomiting accompanied by marked rigidity of the abdominal muscles. A laparotomy was done, and a normal appendix was found. On the fourth day postoperatively polyarthritis developed, and on the tenth day a typical pericardial friction rub was heard. This author commented on the absence of similar case reports in the literature. Hyman,[2] commenting on Geissinger's report, added a second case in a child 6 years of age with a similar acute onset of abdominal pain, tenderness, rigidity and fever. Although the conditions of the abdomen seemed to require surgical intervention, operation was delayed because of cardiac findings. The following day acute arthritis of the ankle appeared, and in the next twenty-four hours fully developed rheumatic fever with large pericardial effusion was present.

Fussel and McKay [3] reported three cases of pericarditis with pain referred to the right iliac fossa. None of these patients was subjected

From the Cook County Children's Hospital and the Department of Pediatrics, University of Illinois.

1. Geissinger, J. D.: Acute Abdominal Pain in Rheumatic Fever, J. A. M. A. **94**:1427 (May 3) 1930.

2. Hyman, A. S.: Abdominal Pain at the Onset of Rheumatic Fever, J. A. M. A. **94**:1782 (May 31) 1930.

3. Fussel, M. H., and McKay, J. A.: Symptoms of Appendicitis in Acute Pericarditis, Am. J. M. Sc. **163**:40 (Jan.) 1922.

to operation, since pericardial findings were manifest on entrance. In one, autopsy revealed plastic pericarditis and a normal appendix.

Wynter [4] reported two cases, one of which was diagnosed perforated gastric ulcer and the second acute appendicitis. Neither revealed pathologic involvement at laparotomy, and in both signs of pericarditis subsequently developed. This author believed the absence of abdominal respiratory movements of value as a diagnostic sign in pericarditis.

Holden [5] cited three cases of a similar nature, in which acute abdominal conditions were diagnosed, in which laparotomy was performed. Pericardial rub developed in each from twenty-four to forty-eight hours postoperatively. He stated that while the relationship of right-sided pneumonia to an acute condition in the abdomen has been stressed, textbooks are silent on the incidence of abdominal symptoms in pericarditis.

In analyzing the mechanism of the production of abdominal symptoms in rheumatic pericarditis, a number of factors must be considered: (1) referred pain from the thorax, (2) rheumatic myositis of the abdominal muscles, (3) rheumatic peritonitis, (4) involvement of the mesenteric glands and (5) true rheumatic appendicitis.

REFERRED PAIN FROM PATHOLOGIC INVOLVEMENT OF THE THORAX

There is considerable divergence of opinion expressed in textbooks regarding the incidence of pain in pericarditis. Holt [6] stated that localized pain and tenderness are usually present in acute rheumatic pericarditis. Norris and Landis [7] stated that pain may be entirely absent or may be of a sharp stabbing character, usually felt over the heart but at times radiating into the abdomen or to the left shoulder or left side of the neck. Allbutt [8] stated that the patient usually complains of a dull ache rather than of acute pain. In other instances, the pain varies from slight discomfort to severe pain aggravated by movement, deep inspiration or cough, localized at times to the epigastrium or radiating to the neck and shoulder blade or shoulder. McKenzie [9] described dry pericarditis as an essentially painless disease,

4. Wynter, W. E.: Absence of Abdominal Respiratory Movements as an Indication of Pericarditis, Clin. J. **42**:185, 1913.

5. Holden, W. B.: Pericarditis, Report of Three Cases in Which Early Symptoms Were Entirely Referred to the Abdominal Cavity, Northwest Med. **19**:230 (Sept.) 1920.

6. Holt and Howland: Diseases of Infancy and Childhood, New York, D. Appleton and Company, 1926.

7. Norris and Landis: Diseases of the Chest, Philadelphia, W. B. Saunders Company, 1918.

8. Allbutt, C., in the Oxford System of Medicine, New York, Oxford University Press, 1920, vol. 2, p. 261.

9. McKenzie, James: Diseases of the Heart, New York, Oxford University Press, 1925.

asserting that there is no distinctive sign characteristic of it other than the presence of a friction rub. When pain is present, accompanying myocardial disease will invariably be found. He said that some writers describe pain as a symptom of pericarditis and that it is possible that a dull ache may be present. When severe pain is aggravated by respiration, it is due to a coincident pleurisy.

From an experimental point of view, there is little literature on pericardial pain. Capps,[10] commenting on the variability of the picture of pain in pericardial pathologic involvement, carried out an investigation to determine what structures within and adjacent to the pericardium were capable of producing pain. This was determined by direct irritation of the pericardium in patients with a large amount of pericardial effusion, a silver wire being inserted through a trocar. Four cases were investigated in this manner. In three instances, no pain was noted on puncture of the pericardium at the level of the fourth interspace. In two punctures at the level of the fifth interspace and in one puncture at the level of the sixth, pain was felt in the neck. Irritation of the serous surface of the visceral pericardium by the wire demonstrated this area to be insensitive to pain, and the serous surface of the parietal pericardium also yielded negative results as far as it could be explored. From his investigations, Capps concluded that dry pericarditis is a painless disease, as McKenzie had stated. Further, the presence of pain in pericarditis indicates involvement of structures outside the pericardium, especially the pleura.

Alexander and his associates [11] presented observations on the sensitivity of the visceral and parietal pericardium in a patient whose heart had been exposed as a result of a pericardiotomy for purulent pericarditis. These authors found that pressure on the inner surface of the parietal pericardium produced pain referred to the chest and abdomen. No other stimulus to the heart, pericardium or diaphragm caused reference of pain to any part of the body.

Unverricht,[12] using the thoracoscope, was able to make observations under physiologic conditions. He found the visceral pleura insensitive to touch, heavy pressure and superficial needle prick. In the case of the parietal pleura, light touch was usually not felt. Pressure and needle prick were felt but not definitely localized. Heat was felt as pain. The diaphragmatic pleura in its central portion gave pain in the neck and shoulder of the same side when stimulated by pressure or

10. Capps, J. A.: Pericardial Pain, Arch. Int. Med. **40**:715 (Nov.) 1927.

11. Alexander, J.; MacLeod, A. G., and Barker, P. S.: Sensibility of the Exposed Human Heart and Pericardium, Arch. Surg. **19**:1470 (Dec.) 1929.

12. Unverricht: Sensibilitätsprüfungen von Pleura und Perikard, Klin. Wchnschr. **6**:855, 1927.

needle prick. In the peripheral portion painful stimuli were noted as an unpleasant sensation in the thorax and upper part of the abdomen of the same side, not definitely localized.

Simenauer,[13] continuing the observations of Unverricht in a larger series of cases, obtained essentially the same results. He was able to test the response to stimulation of certain areas of the pericardium in three cases. Pressure on the parietal pericardium in the region of the apex gave a sense of pressure referred to the left arm especially along its medial aspect, suggestive of the reference of pain in angina pectoris. In a second case, the pericardium of the left ventricle was stimulated, yielding no response to touch and to light pressure. Heavy pressure produced an unpleasant sensation at the level of the sixth rib just inside the midclavicular line. Sticking with a pointed instrument was not felt. In the third case, the pericardium was thickened, and this patient felt no stimuli. The author was unable to draw any definite conclusions regarding pericardial pain from these observations.

In an analysis of the mechanism of abdominal pain in pericarditis, a study of the innervation of the adjacent organs is essential. The researches of Capps,[10] Unverricht [12] and Simenauer,[13] and the clinical observations of such men as McKenzie [9] indicate that the pain in acute rheumatic pericarditis is dependent to a considerable degree on involvement of contiguous structures. The innervation of the diaphragm is derived from two sources, the phrenic nerves and the lower six intercostal nerves. The phrenic nerves are derived principally from the fourth cervical nerves, though they receive fibers from the third and fifth nerves as well. The afferent fibers originate from the cells in the dorsal root ganglions of the third, fourth and fifth spinal nerves. In the lower part of the chest, the phrenic nerves lie between the pericardial pleura and the parietal pericardium, and give off branches that constitute the chief nerve supply of these structures. On reaching the diaphragm, terminal branches spread out over this structure beneath the diaphragmatic pleura. These fibers are distributed to within a few centimeters of the costal margins ventrally and laterally. Branches of the right nerve penetrate the diaphragm and give off rami to the deep muscular structures, the falciform ligament and the peritoneal covering of the upper surface of the liver. The left nerve similarly sends penetrating branches which supply the deep muscular layers of the left dome of the diaphragm and spread out over the central portion of the diaphragmatic peritoneum.

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13. Simenauer, Erich: Die Sensibilität von Pleuren, Perikard, und Peritonealüberzug des Diaphragma mit besonderer Berücksichtigung des Nervus phrenicus, Ztschr. f. Tuberk. **48**:273, 1927.

Experimental data, such as the work of Capps [14] and Capps and Coleman,[15] indicate that the sensory innervation of the anterior two thirds of the diaphragmatic pleura and peritoneum is derived from the phrenic nerves to within a short distance of its ventral and lateral margins. Stimulation of this central diaphragmatic surface gives rise to the familiar shoulder pain. The explanation for this phenomenon lies in the fact that the cutaneous innervation of this area is derived from the branches of the third and fourth cervical nerves. When the sensory fibers of the phrenic nerve are stimulated, pain is referred by the brain to the cutaneous distribution of the third and fourth cervical nerves and not to the position of the diaphragm at all. The explanation for the wide separation of the area of stimulation and the region of reference of pain lies in the developmental history of the diaphragm. This structure is originally formed in the neck and begins to migrate caudally at an early period of intra-uterine life, concomitant with the development of the lung buds. With the full development of the lungs, the diaphragm reaches its permanent position at the lower end of the thorax.[16] In view of this innervation, one would expect shoulder pain to be a common manifestation of pericarditis, as Capps [10] has pointed out.

The nerve supply of the lateral rim of the diaphragm and of the posterior one-third not supplied by the phrenic nerve is derived from the intercostal nerves. Irritation of the posterior one-third and of the lateral and ventral border zones of either surface of the diaphragm causes referred pain over the cutaneous area supplied by the lower six thoracic nerves. This results in referred pain over the upper part of the abdomen and to a lesser extent over the lower quadrants.[17] The developmental explanation for this second innervation lies in the origin of the posterior one-third and the peripheral border of the diaphragm from the adjacent body wall.

In view of the clinical and experimental data at hand, therefore, we may state that the picture of pain in pericarditis is dependent to a considerable extent on involvement of adjacent structures. When the fibrous pericardium and pleura in the region of the diaphragm are involved, pain will occur in the region of the shoulder or neck from irritation of the afferent fibers of the phrenic nerve and reference to

14. Capps, J. A.: An Experimental Study of the Pain Sense in the Pleural Membranes, Arch. Int. Med. **8**:717 (Dec.) 1911.

15. Capps, J. A., and Coleman, G. H.; Experimental Observations on the Localization of Pain Sense in the Parietal and Diaphragmatic Peritoneum, Arch. Int. Med. **30**:778 (Dec.) 1922.

16. Morley, John: Abdominal Pain, Edinburgh, E. & S. Livingstone, 1931.

17. Meyers, J. A.: The Normal Chest, Baltimore, Williams & Wilkins Company, 1927.

the cutaneous area supplied by the third and fourth spinal nerves. When the posterior mediastinum is involved, pain will be referred through the lower intercostal nerves to the abdomen.

Abdominal pain occurs also in the absence of definite evidences of carditis. Coburn,[18] in a study of one hundred and sixty-two patients with rheumatic phenomena, encountered severe abdominal pain in the right lower quadrant more than forty times. In five of these a normal appendix was removed, and shortly afterward unquestionable rheumatic manifestations made their appearance. Recrudescences of rheumatic manifestations later developed in some of these patients, with return of the abdominal pain in the right lower quadrant. Baudet[19] reported a case in which the onset of rheumatic fever occurred with abdominal pain. An appendectomy was done, revealing a normal appendix, and twenty-four hours later typical rheumatic polyarthritis was present. Costedoat[20] cited a similar case in a person with polyarthritis. He suggested the possibility of fixation of the rheumatic virus in the abdominal wall.

Pearson[21] described the abdominal pain of rheumatic fever as an acute sharp pain seated deeply in the epigastrium, recurring in short paroxysms from four to five times daily. The paroxysms were often precipitated by sudden exertion; there was no associated nausea or vomiting, and the incidence bore no relationship to the taking of food. There were no soreness of the abdominal muscles and no tenderness, superficial or deep. Typically, these repeated attacks recurred daily for several days, and then definite rheumatic manifestations appeared. The author attributed this pain to gastric catarrh dependent on the rheumatic infection.

Hutchison[22] described rheumatism or fibrositis of the abdominal muscles as a common manifestation in childhood, and one that may easily simulate acute conditions in the abdomen. He stated that this condition may easily be distinguished by the fact that the pain comes on when the affected muscle is thrown into action, e. g., when the patient tries to sit up in bed without using his hands. There may be considerable tenderness, especially when the muscle is contracted. This

18. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.

19. Baudet: Acute Articular Rheumatism Simulating Appendicitis, Bull. et mém. Soc. d. chir. de Paris **57**:265 (Feb. 28) 1931.

20. Costedoat, M.: Début à forme péritonéale de la maladie rhumatismale, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1353 (Dec. 2) 1929.

21. Pearson, S. V.: Abdominal Pain in Acute Rheumatism, Brit. M. J. **1**: 1120, 1904.

22. Hutchison, R.: Diagnostic Significance of Abdominal Pain in Children, Brit. M. J. **1**:1, 1921.

tenderness differs from that due to inflammation of an underlying organ by the fact that it is also present when the abdomen is grasped or compressed laterally. Still [23] similarly described rheumatic myositis as a common cause of abdominal pain in childhood.

Wood and Eliason [24] recently reviewed the problem of rheumatic peritonitis as a cause of abdominal pain in rheumatic conditions. They cited a considerable number of cases reported in the literature of peritoneal involvement presumably on a rheumatic basis. They reported a case of acute abdominal syndrome in a rheumatic patient in whom laparotomy was done and definite peritoneal pathologic changes found. The appendix was normal. Subsequently, massive pericardial effusion developed. Cultures from both the peritoneal and the pericardial fluid were sterile. On the evidence collected, Wood and Eliason believed that true rheumatic peritonitis may occur more frequently than has been thought heretofore, and may account for the abdominal pain in some cases of rheumatic fever.

The presence of acute adenitis of the mesenteric glands, as pointed out by Brennemann [25] in the case of infections of the respiratory tract, must be borne in mind as a possible causative factor in the abdominal pain of rheumatic fever. The possibility of such involvement of lymphatic structures is repeatedly encountered in the literature.

Finally the occurrence of true acute appendicitis in the presence of acute rheumatic fever is an important possibility which must not be overlooked.

REPORT OF CASES

CASE 1.—*History.*—N. M., a white boy, aged 9, was admitted to the children's surgical ward of Cook County Hospital on Nov. 15, 1928, complaining of pain in the abdomen of four days' duration. He had had a sore throat and headache for two days prior to the onset. The pain was first noted in the region of the umbilicus, and after several hours shifted to the right lower quadrant and the right lumbar region. Nausea was present at the onset, and vomiting occurred once after the administration of a cathartic. Loose stools were present for three days prior to admission.

Examination.—Physical examination of the chest gave negative results, except for roughening of the first sound at the apex of the heart. There was generalized tenderness over the entire abdomen, most marked over the entire right side. Slight rigidity was noted over both upper quadrants, most marked on the right. Peristaltic sounds were present. The child appeared acutely ill, with a temperature of 102.4 F. and a leukocytosis of 23,000. Urinalysis was negative. A diagnosis of acute appendicitis was made and a laparotomy done. The appendix was grossly and microscopically normal, and no peritoneal involvement was present.

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23. Still, G. F.: Common Disorders and Diseases of Children, ed. 2, London, H. Frowde, 1912.

24. Wood, F., and Eliason, E. L.: Rheumatic Peritonitis, Am. J. M. Sc. **181:** 482 (April) 1931.

25. Brennemann, J.: The Abdominal Pain of Throat Infections, Am. J. Dis. Child. **22:**493 (Nov.) 1921.

Course.—Following operation, the boy had a continuous fever of from 101 to 102 F. On the fifth day postoperatively, he complained of pain in the knees. The joints were swollen, hot and tender, and acute rheumatic fever was diagnosed. On the seventh day, postoperatively, cardiac findings were noted, consisting of enlargement, palpable thrill, systolic and diastolic murmur and a loud friction rub over the entire precordium. At this time the boy gave a history of repeated attacks of severe rheumatism. A diagnosis of rheumatic fever with pancarditis was made, and the child was transferred to the medical service. The course was protracted, with several recurrences of fever, pain in the joints, precordial pain and pain in the neck. On Aug. 17, 1929, the patient was finally discharged with a diagnosis of chronic endocarditis with mitral stenosis and insufficiency and aortic regurgitation.

Case 2.—*History.*—C. S., a colored boy, aged 12, was admitted to the surgical service on June 13, 1929, complaining of pain in the right side, headache and pain in the right knee of six days' duration. The onset was abrupt, with sharp stabbing pain in the epigastric region. Shortly afterward, the pain shifted to the right lower quadrant, where it remained constantly, though on one occasion it radiated down both thighs. The child had never had a similar attack previously. Nausea was present but no vomiting. Pain in the right knee had been present during the entire week, and was severe enough to confine the patient to bed. He had had about five of these attacks during the past three years, usually lasting about one month. The bowel movements were normal during the entire course.

Examination.—The boy appeared subacutely ill and in considerable pain. The results of examinations of the heart and lungs were entirely negative. There was tenderness in both lower quadrants of the abdomen, especially on the right, with slight rigidity over the right rectus muscle. Peristaltic sounds were audible. On rectal examination, tenderness was noted in the right lower quadrant. The right knee was painful with much muscular spasm.

Course.—A diagnosis of appendicitis was made, and an appendectomy done. The appendix was grossly and microscopically normal. Postoperatively, the boy had a continuous fever, the temperature being as high as 103 F. On the second day, a pericardial friction rub was heard, and a diagnosis of rheumatic pericarditis was made. The course was stormy, with high fever and considerable cardiac embarrassment showing evidence of patchy consolidation in the fields of both lungs at one time. The patient was finally discharged from the hospital on July 23, with a diagnosis of chronic endocarditis with mitral insufficiency.

Case 3.—*History.*—F. J., a colored boy, aged 13, was admitted to the surgical service on Sept. 4, 1931, complaining of abdominal pain of two days' duration. Three days prior to admission, he had had a headache and pain in the neck. The following morning he noted a diffuse pain in the epigastrium. In a few hours, the pain shifted to the right lower quadrant, where it persisted as a dull ache. There was no associated nausea or vomiting, and the bowel movements were normal.

Examination.—The child did not appear acutely ill or in pain. The temperature on admission was 99.8 F. A systolic murmur was present at the apex and transmitted to the axilla. There was moderate tenderness in the right lower quadrant of the abdomen just to the right of the navel, with no muscular rigidity. There was slight rebound tenderness, and peristaltic sounds were present. The leukocyte count was 22,000, the urine negative.

Course.—A diagnosis of appendicitis was made, and an appendectomy done. Pathologically, the appendix was normal grossly and microscopically. There was no apparent peritoneal involvement at laparotomy. Postoperatively, the child had a constant temperature around 101 F. On the fourth day, he complained of pain

in the left side of the chest, and a definite pericardial friction rub was heard. He was transferred to the medical service with a diagnosis of rheumatic pericarditis. The course was uneventful and he was discharged on October 9, in good condition. On several occasions, he complained of precordial pain and pain in the right side of the neck.

COMMENT

In reviewing these three cases, several factors of diagnostic importance are apparent. Two of the patients gave a definite history of preceding attacks of rheumatic fever. In the third, no rheumatic history was obtained but on physical examination, typical findings of mitral insufficiency were noted. In all three, symptoms suggestive of a generalized systemic infection, such as headache, sore throat and fever, were present before the onset of the abdominal pain. In case 2, definite arthritis of the right knee, which was so severe as to constitute a prominent part of the complaint, was present at the onset.

The character of the abdominal pain in these cases offered the greatest difficulty in differentiating the condition from a surgical condition in the abdomen. In each instance the onset was abrupt, with diffuse pain located in the epigastrium or in the umbilical region and later shifting principally to the right lower quadrant. It was associated with some tenderness in one or both lower quadrants and with slight or no muscular rigidity. Definite localization of tenderness and rigidity was not present in any of these cases. Pain in the neck was complained of in two of the cases, at the onset in one and after the development of signs of pericardial involvement in the other. This pain was prominent enough to be mentioned by the boys without leading questions. Direct questioning as to the incidence of pain in the neck or shoulders and examination for cutaneous hyperalgesia over these areas might be of great diagnostic aid in similar cases.

In the past, the incidence of symptoms simulating an acute condition of the abdomen in pneumonia located in a lower lobe has been stressed. As a consequence, this possibility is kept prominently in mind whenever patients are seen with acute abdominal pain. If the incidence of such a syndrome in rheumatic infections and in acute pericarditis was similarly thought of, undoubtedly the error made in diagnosis would be much less frequent. It may be said, however, that when a reasonable doubt exists as to the presence of acute appendicitis, it is much wiser to err on the side of safety and explore the abdomen.

SUMMARY AND CONCLUSIONS

1. There is considerable variability in the picture of pain in rheumatic pericarditis.

2. Experimental evidence indicates that the presence of pain is dependent on involvement of contiguous structures.

3. The mechanism of its production is discussed.

4. Three cases of rheumatic pericarditis with abdominal symptoms, in which appendectomies were performed, are reported.

5. A rheumatic history, the presence of other rheumatic manifestations, the incidence of pain in the shoulder and the atypical abdominal findings are stressed as of diagnostic value.

6. Pericardial involvement merits equal consideration with pleural involvement, e. g., in pneumonia of the lower lobe of the right lung, in differentiating between acute abdominal conditions, particularly in childhood.

185 North Wabash Avenue.

SARCOMA, MELANOMA AND LEUKOSARCOMA OF THE RECTUM

HERBERT I. KALLET, M.D.
AND
HARRY C. SALTZSTEIN, M.D.
DETROIT

The purpose of this article is to place on record 7 cases of malignant neoplasm of the rectum; 2 of spindle cell sarcoma, 1 of myosarcoma, 3 of melanoma and 1 of lymphosarcoma (leukosarcoma). We are including melanoma within this group of sarcomas notwithstanding the controversy as to whether these growths are of epithelial or of mesoblastic origin.

INCIDENCE

Sarcoma of the rectum, though well recognized and described, occurs infrequently. It has been estimated that only 0.5 per cent of all rectal neoplasms are sarcoma. Weeks [1] estimated that 1 of each 242 sarcomas occurred in the rectum, Williams (quoted by Pennington [2]) 1 in 270 and Lapeyre [3] 1 in 216. Sarcoma occurs with less frequency in the rectum than in other portions of the gastro-intestinal tract. Pennington [2] quoted Corner-Fairbanks that of 175 gastro-intestinal sarcomas only 11 were in the large bowel, 7 of these being in the rectum. These figures undoubtedly include melanotic tumors, which, according to Weeks,[1] "are twice as frequent as other sarcomas of the rectum."

The literature contains relatively few case reports. Weeks [1] stated that "approximately 100 cases are to be found in the literature, and that if doubtful cases were excluded the number would be reduced one-half." Quénu and Hartmann [4] gathered 20 cases in 1899. Bonnett and Chalier [5] reviewed 54 cases in 1911. Lapeyre [3] collected 30 cases (adding 2 personal ones) in 1920. With these exceptions, most of the articles have

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Read before the American Proctological Society, Memphis, Tenn., May 6, 1932.
From the Detroit City Physicians' Office, J. Frank Kilroy, M.D., Director.

1. Weeks, J. H.: Sarcoma of the Rectum, Surg., Gynec. & Obst. **44**:478, 1927.
2. Pennington, J. R.: A Treatise on the Diseases and Injuries of the Rectum, Anus and Pelvic Colon, Philadelphia, P. Blakiston's Son & Company, 1923, p. 505.
3. Lapeyre, N. C.: Le sarcome primitif du rectum, Rev. de chir. **58**:223 and 487, 1920.
4. Quénu, E., and Hartmann, H.: Chirurgie du rectum, Paris, G. Steinheil, 1899.
5. Bonnett, P., and Chalier, A.: Mélanose généralisé à point de depart anorectal, Lyon méd. **116**:917, 1911.

reported single cases, with a more or less general review.[6] Textbooks on proctology rarely mention more than 1 or 2 cases personally observed.

Thompson[7] in 1924 reported 4 cases of sarcoma of the rectum studied at the Mayo Clinic. These represented all such growths seen there up to that time.

Concerning pathologic grouping, Lapeyre[3] divided his 30 cases into: 13 round cell sarcomas, 12 spindle cell sarcomas, 2 lymphosarcomas, 2 myosarcomas and 1 osteosarcoma.

Pennington[2] listed 60 rectal sarcomas as follows: 25 round cell sarcomas, 21 spindle cell sarcomas, 8 lymphosarcomas, 2 myosarcomas, 2 fibrosarcomas, 1 alveolarsarcoma and 1 ossifying sarcoma.

REPORT OF CASES

CASE 1.—*History.*—G. H., a white man, aged 47, a laborer, first seen on April 28, 1931, was referred by the urologic department of the Detroit City Physicians' Office to the proctologic clinic because of a mass in the rectum noted on routine genito-urinary examination. The illness had begun with pain two months before, which seemed to radiate into the penis. It had originated with rectal distress, which had given place for the past month to urogenital pain, which was worse at night. There was no burning on urination or bleeding. When pain in the penis was severe, there was also pain over the left sacral region. Bowel movement was not distressing, nor was there any rectal bleeding. A year and a half ago, the patient had had a painful swelling at the margin of the anus, which subsided spontaneously (probably thrombotic hemorrhoid).

Examination.—On rectal examination, a rounded swelling about 1 inch (2.5 cm.) in diameter was found immediately to the left of the prostate. It was smooth and firm but not stony hard, and very tender on deep palpation. It was somewhat movable underneath the rectal mucosa, projecting into the rectum like a polyp with a wide base. There was no ulceration over the mass.

The patient was admitted to St. Mary's Hospital, and operation was performed on May 5 by one of us (Dr. Kallet).

Operation.—There was a rounded tumor in the left rectal wall lying beneath the mucosa between the sphincter and the prostate. The mass was dissected free and was shelled out in many fleshy particles having the appearance of the inspissated contents of a sebaceous cyst.

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6. (*a*) Saphir, J. F.: Large Spindle Celled Sarcoma of the Rectum, New York M. J. **110**:798 (Nov. 15) 1919. (*b*) Whiteford, C. H.: Sarcoma of the Rectum, J. Path. & Bact. **15**:293, 1910. (*c*) Stimson, C. A.: Spindle Cell Sarcoma of the Rectum, Tr. Am. Proct. Soc., 1927, p. 7. (*d*) Churchman, J. W.: Melanosarcoma of the Rectum, with Report of a Case, Am. J. M. Sc. **155**:639 (May) 1918. (*e*) Kraker, D. A.: Melanosarcoma of the Rectum; Report of a Case, Am. J. Surg. **38**:271, 1924. (*f*) Allen, Victor K.: Melanotic Carcinoma of the Anus, Tr. Am. Proct. Soc., 1931, p. 31. (*g*) Hertzler, A. E.: Perirectal Melanoblastoma Developing in Cutaneous Hemorrhoid, S. Clin. North America **3**:1493 (Dec.) 1923.

7. Thompson, J. W.: Sarcoma of the Rectum, Proc. Staff Meet., Mayo Clin. **2**:241 (Oct. 5) 1927.

The pathologic report was made on May 7 by Dr. J. E. Davis. The mass was described as a soft, velvety, new growth. One section showed connective tissue types of cells arranged in whorls. The cells were not anaplastic, and were very regular. In another section the cells were anaplastic and irregular, almost replacing normal tissue; there were a few giant forms. All of the tissue was highly

Fig. 1 (case 1).—Spindle cell sarcoma.

cellular; there was no differentiation initiating any specific process. The diagnosis was spindle cell sarcoma of the rectum in midripe stage, grade 1 radiosensitivity, grade 3 malignancy.

Course.—On May 14, four radon seeds of 1 millicurie were implanted surrounding the growth. Intensive deep roentgen therapy was given subsequently.

On May 23, the patient was discharged. When again seen on November 1, the mass had disappeared, and he felt well. On December 11, he was in excellent health, and at the time of writing there has been no local recurrence.

CASE 2.—*History.*—M. F., a white youth, aged 17, a university student, was admitted to Harper Hospital on Feb. 14, 1931, to Dr. Kallet's service. His present illness had begun six weeks before, with pain on defecation, radiating down the left leg like sciatica. This had become increasingly severe, so that he could not sleep, and a diagnosis of osteomyelitis of the hip had been considered. The family history showed that the father had died of carcinoma of the rectum at a rather early age.

Fig. 2 (case 2).—Spindle cell sarcoma.

Examination.—Examination showed a young man of good nutrition apparently not acutely ill. On rectal examination, a mass about the size of a hen's egg could be felt beneath the mucosa of the anterior rectal wall overlying the region of the left seminal vesicle. The mass was fluctuant and somewhat tender. The prostate was normal.

Operation.—On the day of admission an incision was made by one of us (Dr. Kallet) through the anal mucosa into the mass. It lay deep in the presacral region,

was firm like a neoplasm and covered with rectal mucosa. Several ounces of grumous bloody fluid containing particles of tumor tissue were evacuated.

Microscopic examination was made by Dr. P. F. Morse, who diagnosed the mass as a spindle cell sarcoma of a very malignant type.

Course.—Following his discharge from the hospital, the patient consulted Dr. G. E. Pfahler in Philadelphia. There intensive deep roentgen therapy and radium needle implantation were given. The tumor proved unresponsive to this treatment. On May 15, he returned to Detroit. At that time there were marked cachexia and

Fig. 3 (case 3).—Myosarcoma. Section from peripheral portion of tumor. Other areas showed marked anaplasia.

excruciating pain. There was a large sloughing mass in the rectum which practically occluded the lumen. Colostomy was recommended, and the patient entered the University Hospital at Ann Arbor. There a cordotomy was performed (May 21), followed shortly by a colostomy (June 9). The patient was relieved from pain until his death, which occurred on June 22.

Case 3.—*History.*—A. T., a man, aged 46, first seen on Feb. 8, 1927, in the proctologic clinic, Detroit City Physicians' Office, complained of severe constipation and rectal protrusion. For several years he had had infrequent stools and had taken Sal Hepatica every two or three days. Three months before, a small, hard mass protruded on defecation, returning spontaneously. Since then the stools

had been soft like butter, but there was no diarrhea. Bowel movement had been growing more difficult, and on straining, the patient had had a sensation as if a mass like an egg were crowding into the anus. Sometimes this mass protruded. There was little pain.

Examination.—Examination showed a well developed man in good nutrition. A hard mass was felt externally to the right side of the anus. The sphincter was spastic. On digital exploration, beginning about three fourths of an inch (1.9 cm.) above the anus, a large, hard mass was felt extending to the right and bulging into the rectum. The upper limit of the mass could not be palpated. A deep trough was felt on either side of the mass where it joined the rectum. The tumor seemed to fill the entire presacral space and encroached so on the lumen of the rectum as practically to close it. The mucosa over the tumor appeared intact.

The patient was referred to the Detroit Receiving Hospital, and was admitted to the service of Dr. L. J. Hirschman on February 9.

Operation.—On the day following admission, operation was performed by Dr. Hirschman. A three and one-half inch (8.9 cm.) incision was made, beginning at the outer margin of the external sphincter. The incision was carried into the gluteal area until the mass was reached. This was freed from surrounding tissues by blunt dissection. The portion adherent to the upper surface of the rectum was clamped and cut away, thus removing a small area of rectal tissue. A large iodoform pack was used.

Pathologic examination was made by Dr. O. A. Brines. The specimen weighed 1,400 Gm. and measured 12 cm. in diameter. Microscopic examination showed a new growth of smooth muscle arranged in interlacing bundles and containing a moderate amount of fibrous tissue. A section from the central portion of the tumor showed conspicuously immature cells with marked anaplasia. Another section from the periphery showed all mature cells of leiomyoma. The diagnosis was myosarcoma of the rectum.

Course.—There was improvement following the patient's discharge from the hospital. Constipation was relieved, and there was gain in weight. Within two months, however, a yellowish purulent discharge developed from the rectum, with some bleeding. Constipation recurred, with loss of strength.

On September 23, the patient was readmitted to the Detroit Receiving Hospital. Rectal examination showed a long, irregular scar posteriorly. An irregular mass was palpable on digital exploration, almost filling the rectum.

On October 12, a midline colostomy was performed, and the patient was referred for deep roentgen therapy.

On Jan. 30, 1928, the rectal mass was increasing in size, and the patient had an irregular septic temperature.

On March 10, a raw mass larger than a fist obscured the anal canal. It was covered with whitish exudate and had eroded into the left buttock. It looked like raw meat and had a foul odor.

Severe hemorrhage occurred, with death on March 11.

Case 4.—*History.*—Mrs. A. B., aged 47, was admitted to the Harper Hospital on June 18, 1920, to the service of Dr. Angus McLean, with the complaint of severe vaginal and rectal discharge since the last menses three weeks before, and protrusion from the rectum at defecation.

Operation.—On July 5, local resection was made of a gangrenous rectal polyp, with curettement of the base.

The pathologic report was made by Dr. P. F. Morse, who returned a diagnosis of very malignant melanosarcoma of the rectum.

Course.—The patient made a good recovery and was symptom-free for four years. At that time signs of localized intracranial pressure developed, and she died one year later. There was no local recurrence of the original mass.

CASE 5.—*History.*—Mrs. M. A., aged 58, a housewife, consulted one of us (Dr. Kallet) on June 21, 1931, with the history of a sudden attack of constipation and rectal pain two months before that had not been aggravated by bowel movement.

Fig. 4 (case 4).—Highly pigmented melanoma.

Two weeks later she began to notice bright red blood in the stools. Since that time she had required mineral oil in large quantities. Bowel movements were small and in thin pieces. She had lost 13 pounds (5.9 Kg.) in two months. She had had a hysterectomy nine years before. She complained of severe hemorrhages from puberty to the menopause.

Examination.—The rectum externally was normal. There was a hard, nodular mass on the right side of the rectum, located 1 inch (2.5 cm.) above the sphincter, reaching into the anal canal and involving the right side of the rectovaginal septum.

Fig. 5 (case 5).—Cellular melanoma. *A* shows the early lesion with alveolar round cell arrangement and very little pigment; B shows marked pigmentation (metastatic growth).

The growth was about 2 inches (5 cm.) in diameter, well defined and slightly ulcerated. The patient was referred to Harper Hospital on June 22, and was admitted to the service of Dr. L. J. Hirschman.

Operation.—On June 26, Dr. Hirschman made a perineal extirpation of the rectum. The growth, with a portion of the posterior vaginal wall, was excised. The resection was carried up to the sigmoid; the sigmoid end was brought down and

Fig. 6 (case 6).—Melanoma. Note the spindle cell arrangement.

sutured to the skin of the anus, preserving the sphincter. The rectovaginal septum was repaired with interrupted catgut stitches.

The pathologic diagnosis was melanosarcoma. The melanin was very scant.

Course.—Within a week, a rectovaginal fistula developed. Two attempts were made to repair this. About October 1, a hard visible mass about the size of a cherry developed in the right inguinal region. At the same time, a hard ulcerated mass, 1½ inches (3.8 cm.) in diameter, was noted to the left of the anal orifice. Biopsy of tissue from both of these masses showed advanced metastatic melanosarcoma. Both masses were deeply pigmented and almost black. The patient was

severely anemic, and was given large doses of ventriculin. Deep roentgen treatment was instituted locally.

On Jan. 4, 1932, the patient was up and about. The anemia showed some improvement, but she was still extremely weak.

CASE 6.—*History.*—J. M., a white man, aged 61, a painter, was admitted to Harper Hospital, Dr. L. J. Hirschman's service, on March 23, 1928. His illness had begun about three years before with rectal protrusion and bleeding. Two years before he had been operated on by Dr. Hirschman for a large rectal neoplasm, which pathologically was melanosarcoma. The growth and postsacral glands were excised, and he improved for eighteen months. At that time, pus appeared in the stools, severe constipation was present, and defecation was painful. There was no bleeding. There had been a loss of 10 pounds (4.5 Kg.) in weight. Urination had become difficult, and there were recent incidents of acute retention.

Examination.—Examination showed a thin, somewhat emaciated man. Rectal examination showed melanotic spots on the skin around the anus. A polypoid mass presented on the posterior rectal wall. There was a hard, fixed mass on the anterior wall of the rectum, in which the prostate seemed included.

Operation.—At operation on March 24, Dr. Hirschman found a growth the size of a child's head situated between the fundus of the bladder and the prostatic and pelvic floor. The sigmoid was densely adherent. The mass was removed with great difficulty through a transverse incision. A hypertrophied infected gland was removed posterior to the anal canal.

Microscopic examination showed a very malignant spindle cell melanosarcoma.

Course.—Postoperatively, there were hiccup, elevation of the temperature in the evening, pain in the lower part of the abdomen and retention of nitrogen. Death occurred on April 6, twelve days after operation.

CASE 7.—*History.*—J. M., a white man, aged 51, a laborer, was first seen by one of us (Dr. Kallet) on November 15, 1927. He was referred by Dr. Norman K. H'Amada, complaining of pain on defecation, tenesmus and bleeding from the rectum. Four weeks previously he had a chill and began to have pain in the buttocks. For the two following weeks he was extremely constipated, his bowel movements being pencil-like. Then the constipation was replaced by severe diarrhea. There were six or seven movements an hour. He passed considerable flatus, blood and mucus and had an apparent urge to move the bowels continuously. Each movement was accompanied by pain so severe as to be unbearable. He felt himself growing weak and stated that he had lost 7 inches (17.78 cm.) from his belt line.

Examination.—Examination disclosed a well developed and well nourished man of middle age, who was weak and somewhat pale. He appeared acutely ill. The teeth were carious, and the gums were in poor condition.

The cervical and axillary glands were slightly enlarged, and the inguinal glands were markedly enlarged. The abdomen was distended and generally tender. No masses were felt.

On digital examination of the rectum a mass could be felt which originated about 2 inches (5 cm.) above the anus and filled the entire ampulla. The lumen of the rectum was almost obliterated. The mass was annular, firm and tender. It gave the impression of being submucosal in origin.

Proctoscopic examination showed that the mucosa of the rectum seemed to be markedly congested and presented many petechial hemorrhages. No effort was made to pass the sigmoidoscope through the tumor.

Fig. 7 (case 7).—Lymphosarcoma (leukosarcoma). *A* shows lymphatic infiltration of pelvic cellular tissues; *B*, high power magnification.

Course.—The patient was admitted to Providence Hospital on November 17. The course in the hospital was rapidly downward. On admission there were a few petechial hemorrhages over the lower part of the abdomen and a few on the chest, although none had been noted at the first examination. Within the next two or three days, there were purpuric spots over the entire body. Four days after admission there was a slight oral hemorrhage. Some epistaxis, hematuria and bloody diarrhea (from eight to ten stools per hour) developed. The patient became extremely weak. The hemorrhages from all the body orifices increased, and the severe pain in the rectum required heavy doses of morphine for relief.

Dr. A. Kunin made an examination of the blood. Dr. W. L. Brosius' report on a smear was: "The large mononuclear cells of the lymphocytic group closely resemble the cells of the tumor."

The red blood cells numbered 4,900,000, and the hemoglobin was 75 per cent. The results of the differential counts were:

Date	White Blood Cells	Polymorphonuclears, per Cent	Small Mononuclears, per Cent	Large Mononuclears, per Cent	Eosinophils, per Cent
11/18/27	38,000	23	6	69	2
11/20/27	56,400	13	5	80	2
11/23/27	60,000	16	6	77	1

Emergency colostomy was performed for impending intestinal obstruction on November 26 by one of us (Dr. Kallet). Under local anesthesia the transverse colon was rapidly pulled into the abdominal wound, fixed and not opened.

Rapid abdominal exploration revealed no further masses.

Following operation there was a severe nosebleed, and the urine passed was practically pure blood. The patient died four hours later.

The pathologic report was made by Dr. Brosius. Local removal of a portion of the tumor post mortem showed microscopically an extensive infiltration of the rectal mucosa, muscle, fibrous layers and prostate gland. It was a solid tumor composed of uniform rounded cells with round, deep-staining, coarsely granular nuclei and a scanty amount of relatively clear cytoplasm essentially lymphoid, resembling the lymphocyte of the lymph node. Anaplasia was not very marked, but invasiveness was decidedly marked. Examination of the blood smear made on November 23, showed 77 per cent of large mononuclear cells of the lymphocytic group, which closely resembled the cells of the tumor.

The diagnosis was leukosarcoma of Sternberg.

COMMENT

The clinical manifestations and progress of these patients conform in general to the description found in most textbooks. However, certain points may merit emphasis.

Both sarcoma and melanotic growths arise beneath the mucosa, ordinarily either in the anal canal or in the lowest part of the ampulla. It is often stated that these growths generally originate in the posterior wall. However, six of our cases were on the anterior wall. When located anteriorly, the first symptoms may be due to pressure on the structures at the neck of the bladder. The patient in case 1 consulted a urologist for pain radiating into the penis. Case 6 presented involvement of the prostate and bladder wall.

In several of the histories, pain was a prominent early symptom. In case 1, as noted, it radiated to the penis. In case 2 it radiated along the left sciatic nerve and was so excruciating that the patient could not sleep. In case 4 there were terrific tenesmus and rectal spasm out of all proportion to that seen in early rectal cancer. The patient in case 5 also had severe rectal pain.

The first objective manifestation—the mass beneath the mucosa—is early of insignificant appearance and may be confused with a benign polyp or hemorrhoid. This emphasizes the importance of pathologic examination of all excised hemorrhoid tissue.

The mucosa remains intact as the early growth of the neoplasm proceeds. With straining at stool, the tumor frequently develops into a polyp, usually with a short pedicle which may protrude and recede painlessly on defecation. The first manifestation in case 3 was a small mass which was extruded with each bowel movement. In case 4 a bulging gangrenous rectal polyp proved to be melanoma.

More often the growth develops locally, forming a mass almost indistinguishable from carcinoma. In sarcoma the mucosa tends to remain intact longer, and ulceration occurs late. There is not the marked obstruction seen in some rectal cancers. Digital examination gives the impression that the lumen of the rectum is being compressed by an extra mucosal mass, whereas in carcinoma there is rather a sensation of direct involvement of the mucosa, with early crater formation. Occasionally sarcoma develops as a semifluctuant granulomatous mass which clinically invites incision for drainage. (When incision was made in case 2 a grumous, sanguineous fluid was discharged containing many fleshy particles).

Melanoma.—In our cases there was little distinguishable difference between the clinical course of melanoma and of sarcoma. As a matter of fact, even a histologic differentiation may be difficult, for melanomas tend to develop spindle cells, and at first their pigment may be absent or so scanty as to escape detection. The metastatic deposits, on the contrary, usually exhibit heavy pigmentation, as may older tumors. Case 5 showed very faint pigment granules, scarcely discernible in the first section, while the later metastases were densely pigmented.

The origin of these growths (melanotic) is at present a matter of controversy. Several proctologists and many dermatologists classify them as of epithelial derivation—melanocarcinomas. However, Ewing,[8] in a careful critical review, considers that Soldan and more recently Masson have proved more or less conclusively that the original melanoma cell is of mesoblastic or neuro-ectodermal, certainly not epithelial, origin. He believes that the nevus cell is derived from and belongs to the

8. Ewing, James: Problems in Melanoma, Brit. M. J. **2**:852 (Nov. 22) 1930.

peripheral sensory nerve end apparatus. These pigment-bearing cells may and often do enjoy a more or less independent existence, and while they are more numerous in regions where the tactile sense is highly developed, such as the nail-bed, anus or orbit, they may be found in the skin or mucous membrane of any portion of the body.

Leukosarcoma.—The lymphatic neoplasm (case 7), on the other hand, was a distinct clinical entity: a rapidly fatal blood dyscrasia with hemorrhages from all mucous membranes, a steadily rising white cell count characteristic of lymphatic leukemia and a large lymphomatous mass surrounding the rectum. Sternberg has applied the term leukosarcoma to this condition. He differentiates three grades of lymphatic malignancy: (1) lymphatic leukemia as classically described, with a characteristic blood picture; (2) lymphosarcoma, a lymphomatous tumor without the leukemic blood picture, and (3) leukosarcoma, a local malignant lymphomatous tumor with the blood picture of lymphatic leukemia.

There is considerable objection among some pathologists, Ewing, Herxheimer and others, to the separation of these tumors into a special group. They contend that the majority of these growths represent only an excessive hyperplasia of the lymphoid tissue such as is observed in lymphatic leukemia.[9] However, the term is still used. In our case, although there was a definite mass constricting the lumen of the rectum, the microscopic picture was more nearly that of a leukemic infiltration of the pelvic cellular tissues.

Leukosarcoma has been described in various locations, including the gastro-intestinal tract. Warthin reported its occurrence in the ileum, and Moritz in the cecum. Weiss [9] has also described it in the cecum. We have been unable to find a similar rectal neoplasm on record.[10]

Prognosis.—Most authors state that sarcoma and melanoma of the rectum are invariably fatal. Very few patients have survived more than two years following any treatment. It has been noted that sarcomas of the rectum do not spread locally as carcinomas do. There is a rapid extension to the inguinal nodes and then to the liver, lungs and other viscera. Most authors recommend wide radical resection. Churchman [6d] has advised preliminary laparotomy before extensive resections are undertaken to determine the presence of abdominal metastasis, which he believes will be found in 80 per cent of the cases.

Radium and roentgen therapy have been used both alone and in combination with surgical measures, but their value is as yet not definitely established. So far as we have been able to determine, no cures have been reported.

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9. Weiss, Emil A.: Case of Localized Leucosarcomatosis of the Ascending Colon and of the Cecum, J. Lab. & Clin. Med. **16**:567 (March) 1931.

10. Flashman, David H., and Leopold, Simon S.: Leukosarcoma, Am. J. M. Sc. **177**:651, 1929.

The results of our series were as follows:

Case 1, spindle cell sarcoma: The patient is well and free from recurrence eight months after local resection, implantation of radon seeds and deep roentgen therapy.

Case 2, spindle cell sarcoma: There was a rapidly downward course, with death in four months, despite local removal and intensive radiation.

Case 3, myosarcoma: The course was progressively downward despite operation and deep roentgen therapy, death occurring thirteen months after local resection.

Case 4, melanoma: The patient was symptom-free for four years after local removal. Death occurred five years post operatively, following cerebral symptoms, perhaps metatases. There was no local recurrence.

Case 5, melanoma: The patient is alive seven months after resection and deep therapy, but is rapidly failing.

Case 6, melanoma: There was improvement for eighteen months following local resection. Death occurred two months later, following operation for recurrence.

Case 7, leukosarcoma: The patient died six weeks from the onset, with symptoms of acute lymphatic leukemia.

SUMMARY

1. Seven cases of unusual rectal tumors, three sarcomas, three melanomas and one leukosarcoma, are reported.

2. The clinical features and course of these neoplasms are discussed.

EXPERIMENTAL THYROID HYPERPLASIA

AN INCREASED INTAKE OF CHLORIDE COMBINED WITH A DIET DEFICIENT IN IODINE AS A FACTOR

JAMES S. HIBBARD, M.D.
NEW YORK

At the present time endemic goiter is commonly placed in the category of a deficiency disorder, and attention is being focused on iodine as the lacking element. This is a natural tendency because of its apparent therapeutic value. Hellwig [1] opposed this point of view and stated that a positive factor and not a deficiency of iodine is the essential cause. He believes that an increased intake of calcium chloride represents a positive agent, and if combined with a deficiency of iodine hyperplasia of the thyroid will result.

My purpose in this paper is to report an experimental study on thyroid hyperplasia produced in a relatively nonendemic region based on the theory that calcium chloride represents a positive factor.

REVIEW OF THE LITERATURE

Knappenburg,[2] in 1919, reported negative results in a series of rats fed on water containing but a small amount of iodine. His experiments were conducted in Holland, a goiter-free region, the water being supplied from an endemic area. A year later, Houssay [3] conducted a similar experiment in Buenos Aires, another nongoitrous region, and stated that goiter developed in only two rats, from several lots of twenty each, when supplied by water from a goitrous region. McClendon [4] discounted this work, saying that the iodine content of the food was not determined. In 1922, McClendon and Williams,[5] working in Minne-

From the Laboratories of Surgery, College of Physicians and Surgeons, Columbia University.

1. Hellwig, C. A.: Iodine Deficiency and Goiter, Arch. Path. **11**:709 (May) 1931.

2. Knappenburg, B. D. G.: Geneesk. bl. u. klin. en lab. v. d. prakt. **21**:300, 1919; quoted by McClendon (footnote 4).

3. Houssay, B. A.: Rev. d. Inst. bact. **2**:629, 1920; quoted by McClendon (footnote 4).

4. McClendon, J. F.: Distribution of Iodine with Reference to Goiter, Physiol. Rev. **7**:189 (April) 1927.

5. McClendon, J. F., and Williams, Agnes: Experimental Goiter and Iodine in Natural Waters in Relation to Distribution of Goiter, Proc. Soc. Exper. Biol. & Med. **20**:286, 1922-1923.

sota, an endemic area, produced changes in the thyroid gland in rats fed on a diet containing ten parts of iodine per billion parts of dry food. Hayden, Wenner and Rucker,[6] working in the same area, confirmed their results by producing thyroids twice the normal size in rats fed on a similar diet. Tanabe,[7] in southern Germany, also obtained hyperplasia in the thyroids of rats fed on a diet poor in iodine, but again, as Hellwig pointed out, "domesticated animals in goitrous areas incur goiters spontaneously."

Hellwig [1] failed to produce any changes in the thyroid gland in Kansas, a goiter-free area, when he used the same diet prescribed by Tanabe, and partially on these results he based his conclusions that the essential cause of goiter must be a positive agent rather than a deficiency of iodine alone. Orr's [8] extensive geological studies point to this conclusion. He studied the iodine content of the foodstuffs and soil in England and Scotland, and found no correlation between a deficiency of iodine in the food and the occurrence of endemic goiter. Wegelin [9] insisted that atrophy of the thyroid gland should result from a lessened intake of iodine since iodine stimulates the thyroid gland. Hellwig's experiments confirm this view, both grossly and microscopically. Following this assumption, he produced marked hyperplasia in rats' thyroids by using a diet high in calcium chloride and low in iodine. Hellwig [1] also wrote that Tanabe recently produced pronounced hyperplasia apparently from a diet high in calcium and low in iodine. Added evidence as to the value of calcium chloride as a positive agent is the work brought forth by McCarrison,[10] who, during a geological study of endemic goitrous areas in northern India, found that the drinking water was obtained from areas containing large deposits of limestone.

EXPERIMENTAL DATA

Three groups of rats were studied in the first experiment. Group A received a normal diet, group B received a diet low in iodine, consisting of pearl barley, distilled water and 2 Gm. of raw beef every third day. Based on the diets used by Hellwig,[1] group C received barley, 2 Gm. of raw beef every third day and a 2 per cent solution of calcium chloride, instead of the distilled water. A determina-

6. Hayden, E. M.; Wenner, W. T., and Rucker, C. W.: Production of Goiter in Rats by Restricted Iodine Feedings, Proc. Soc. Exper. Biol. & Med. **21**:546, 1923-1924.

7. Tanabe: Experimenteller Beitrag zur Aetiologie des Kropfes, Beitr. z. path. Anat. u. z. allg. Path. **73**:415, 1925.

8. Orr, J. B.: Iodine Supply and the Incidence of Endemic Goiter, Medical Research Council Special Report Series, No. 154, London, His Majesty's Stationery Office, 1931.

9. Wegelin, quoted by Hellwig (footnote 1).

10. McCarrison, R.: The Thyroid Gland in Health and Disease, London, William Wood & Company, 1917.

tion of the iodine, made by Dr. Roe Remington,[10a] in the barley used in all experiments showed thirteen parts per billion. The housing of the rats during the experiment consisted of heavy mesh wire cages, with a raised floor and no bedding. The drinking water was contained in special drinking flasks to prevent contamination. The animals were killed on the one hundred and twelfth day, and the thyroids were dissected, weighed and sectioned for microscopic study. From table 1 and 2, it is evident that the thyroids in group B weighed much less than those in group A, both absolutely and in comparison with the body weight. Microscopically (fig. 2), they showed very abundant and deeply staining colloid, low epithelium and moderately small acini. This is in contradistinction to the pathologic picture of early mammalian goiter, which was described by Langhans and Wegelin,[11] Marine and Lenhart [12] and Hellwig [1] as showing extremely

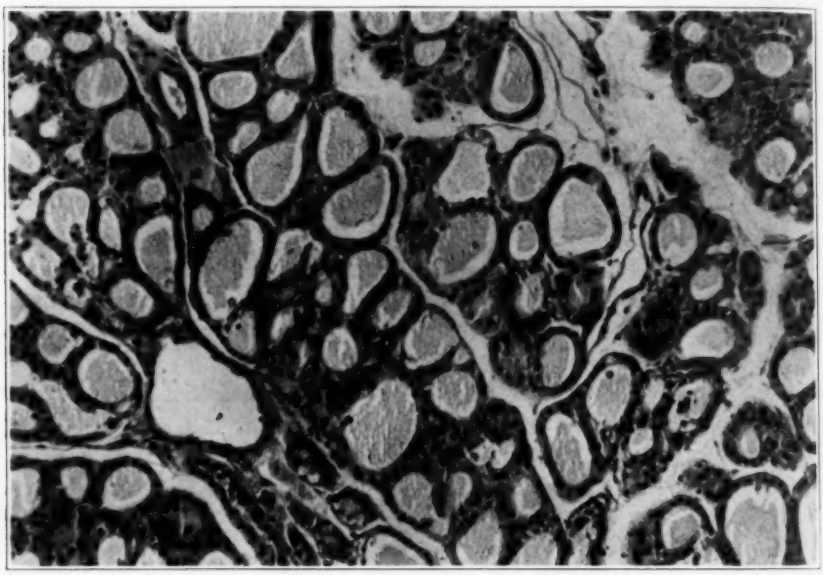

Fig. 1.—Normal thyroid of a rat grown in a relatively nonendemic region, New York.

small acini, a marked decrease in colloid, columnar epithelium with plications and papillae, mitotic figures and hyperemia of the gland. The results in group B correspond with Hellwig's work and also substantiate Wegelin's theory.[9] From a comparison of group C (table 3) and group B (table 2), it is obvious that the glands produced on the diet low in iodine and high in calcium chloride are much larger. In comparison with the normal, although the thyroids in group C are only slightly heavier absolutely, they are moderately greater when compared with

10a. Remington, Roe E.: Personal communication.

11. Langhans and Wegelin: Der Kropf der weissen Ratte, Bern, Paul Haupt Ackademische Buchhandlung, 1919; quoted by Hellwig (footnote 1).

12. Marine, D., and Lenhart, C. H.: Relation of Iodine to the Structure of Human Thyroids, Arch. Int. Med. **4**:440 (Nov.) 1909.

the body weight. Five of the nine rats showed a definite hyperplasia of the thyroid gland as evidenced by the small size and irregularity of the acini, decrease in the colloid, high cuboidal or columnar epithelium with plications, numerous areas of solid cells, some desquamation and hyperemia (fig. 3).

TABLE 1.—*Group A, Normal Diet*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid*	Hyperemia*	Hyperplasia*
A-1	200	M	18	Large and moderate size	Flat and low cuboidal	3	0	0
A-2	201	M	30	Large and moderate size	Low cuboidal	3	1	0
A-3	209	M	20	Large and moderate size	Flat and low cuboidal	3	0	0
A-4	255	M	20	Large and moderate size	Flat and low cuboidal	3	1	0
A-5	166	M	31	Moderate size	Flat	3	0	0
A-6	204	M	40	Large size	Flat and low cuboidal	3	0	0

* In this and the following tables, colloid, hyperemia and hyperplasia are graded as follows: 0, none; 1, slight; 2, moderate, and 3, marked.

TABLE 2.—*Group B, Diet Low in Iodine With 3 Gm. of Beef Every Third Day*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
B-1	209	M	16	Moderate and small size	Flat and low cuboidal	3	0	0
B-2	204	M	15	Moderate and small size	Flat and low cuboidal	3	0	0
B-3	164	M	16	Moderate and small size	Flat	3	0	0
B-4	150	M	15	Moderate size	Flat	3	0	0
B-5	133	M	22	Moderate and small size	Flat	3	0	0

TABLE 3.—*Group C, Diet Low in Iodine and High in Calcium Chloride With 3 Gm. of Beef Every Third Day*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
C-1	168	M	25	Very small; solid areas	Cuboidal with budding	1	2	2
C-2	179	M	35	Very small; solid areas	Cuboidal, budding, papillae	1	2	2
C-3	181	M	36	Large and moderate size	Flat	3	0	0
C-4	130	M	33	Very small; solid areas	High cuboidal	1	2	3
C-6	194	M	39	Moderate size	Cuboidal and budding	2	1	1
C-7	146	M	23	Small; solid areas	High cuboidal	1	2	3
C-8	169	M	24	Moderate size	Flat and low cuboidal	3	0	0
C-9	223	M	40	Moderate size	Cuboidal	2	1	0
C-10	164	M	34	Moderate size	Cuboidal	3	0	0

The second experiment consisted of five more rats in group B, (table 4) and five more in group C (table 5). The diet was the same as in the preceding groups, except that the raw beef was withheld. The results obtained correspond exactly with those of the previous series, i. e., the rats on the diet low in iodine showed no thyroid hyperplasia, whereas the group on the diet low in iodine and high in

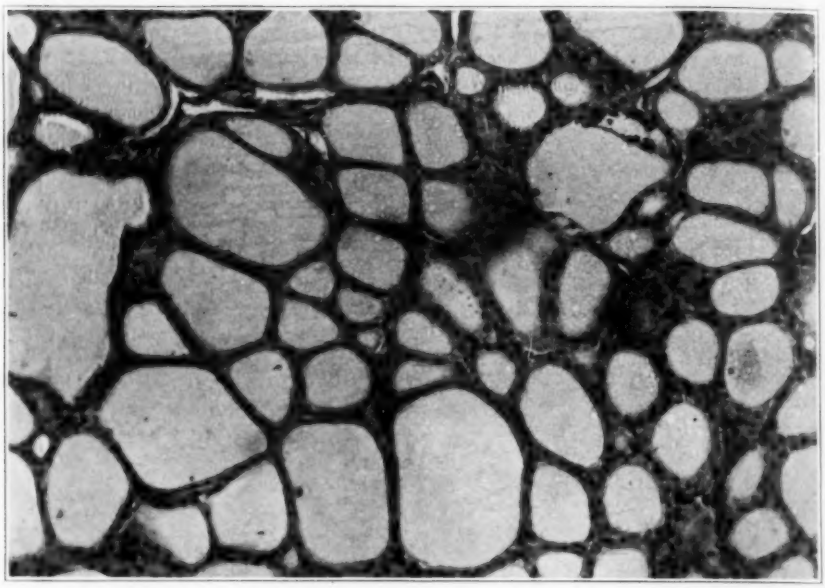

Fig. 2 (rat, B-8).—Thyroid after administration of a diet low in iodine for one hundred and twelve days.

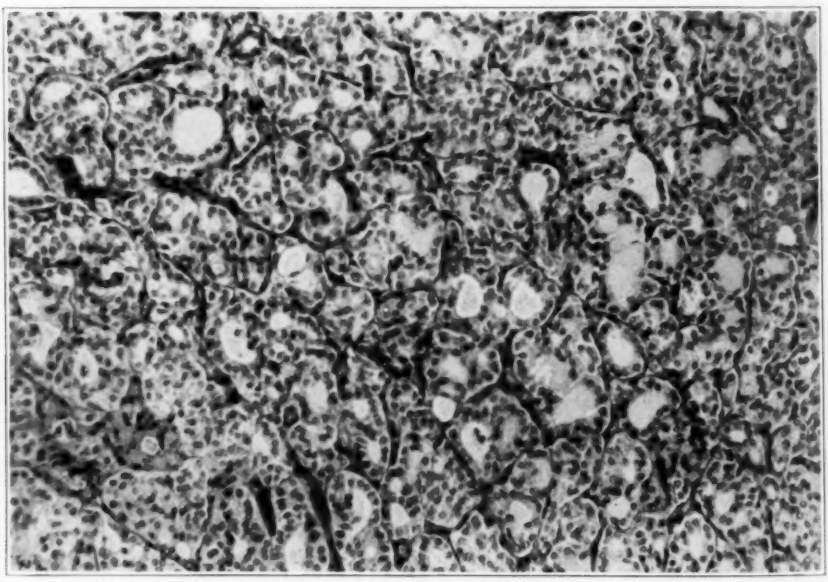

Fig. 3 (rat, C-23).—Thyroid hyperplasia produced by a diet low in iodine and high in calcium chloride.

calcium chloride showed definite changes. The results obtained in these experiments correspond closely with Hellwig's, although he was able to demonstrate more pronounced changes in his entire group.

Since ten of the fourteen animals showed definite hyperplasia on the diet high in calcium chloride and low in iodine it was thought advisable to run experiments on a larger group. Also, since the calcium was thought to be the active principle, it follows that hyperplasia would be produced even though a different calcium-containing ingredient was used. Conversely, changes would not be produced if the calcium ion was replaced. In accordance with these deductions, a third series of experiments was run. The same precautions were carried out as in the preceding series. The animals were allowed to live from ninety to one hundred

TABLE 4.—*Group B, Diet Low in Iodine*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
B- 6	162	M	16	Moderate and small size	Flat	3	0	0
B- 7	135	M	26	Moderate and small size	Flat and low cuboidal	3	0	0
B- 8	169	M	26	Moderate and large size	Flat	3	0	0
B- 9	126	M	18	Small size	Flat	3	0	0
B-10	132	M	20	Small and moderate size	Flat	3	0	0

TABLE 5.—*Group C, Diet Low in Iodine and High in Calcium Chloride*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
C-11	130	M	35	Very small and irregular	Cuboidal	1	3	2
C-12	120	M	28	Solid areas; irregular and very small	Cuboidal	1	2	2
C-13	132	M	32	Very small and irregular; solid areas, and areas showing no acinar form	Cuboidal	1	2	2
C-14	142	M	34	Same as for preceding animal	Cuboidal	1	3	2
C-15	138	M	29	Very small and irregular; solid areas	Cuboidal	1	3	2

and one days, after which their thyroids were dissected and sections made for microscopic study. Three groups of rats were distinguished in this series. Group C (table 6), twenty-nine more animals, received a diet low in iodine and high in calcium chloride. Twenty-two thyroids showed a definite hyperplasia, as shown in the previous group C.

Group D (table 7), twenty rats, received a diet consisting of pearl barley and a 5.4 per cent solution of calcium lactate, to serve as drinking water. The results were surprising, as none of the rats showed changes in the thyroid gland, although the calcium ion had been retained in the drinking water (fig. 4). Group E (table 8), sixteen animals, received a diet of pearl barley and a 3 per cent solution of sodium chloride. Likewise, the results obtained in this group were entirely unexpected. Definite hyperplasia, as demonstrated in figure 5, occurred in fifteen of the thyroids. The changes were very similar to the findings obtained in the group fed on a diet low in iodine and high in calcium chloride, although the calcium ion had been replaced by sodium.

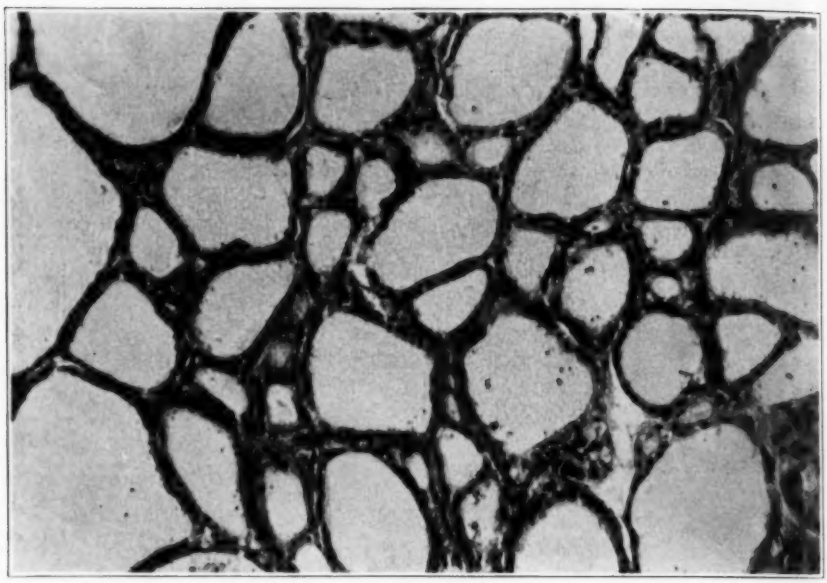

Fig. 4 (rat, D-18).—Normal thyroid after a diet low in iodine and high in calcium lactate.

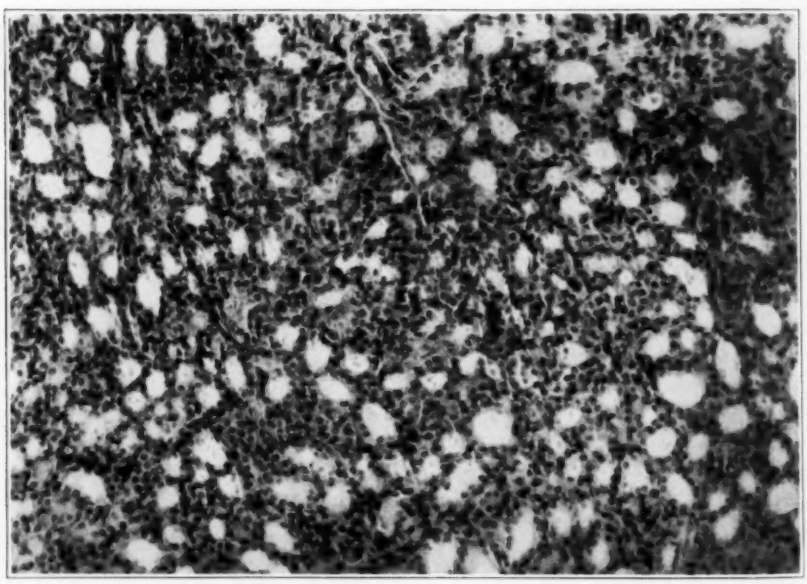

Fig. 5 (rat, E-16).—Thyroid hyperplasia produced by a diet low in iodine and high in sodium chloride.

TABLE 6.—*Group C, Diet Low in Iodine and High in Calcium Chloride*

Rat No.	Sex	Weight, Gm.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
C-16	M	130	Very small; irregular and tubes	High cuboidal	1	3	2
C-17	F	135	Solid areas; very small and irregular	High cuboidal	1	3	2
C-18	M	140	Very small; many solid areas	High cuboidal and columnar	1	2	2
C-19	M	138	Moderate and small	Cuboidal	1	1	0
C-20	M	130	Small; tubes and solid areas	High cuboidal	1	2	2
C-21	M	135	Very small; tubes and solid areas	Columnar	1	2	3
C-22	M	140	Small, moderate; solid areas, buds	High cuboidal	1	3	2
C-23	M	130	Small; tubes, solid areas and buds	Cuboidal and columnar	1	3	3
C-24	M	170	Moderate and large size	Low cuboidal	2	1	0
C-25	M	180	Moderate and large size	Low cuboidal	2	1	0
C-26	M	120	Moderate and small size; budding	High cuboidal	2	3	1
C-27	F	120	Moderate, small; tubes, budding	High cuboidal	1	2	2
C-28	M	150	Moderate and small size	Cuboidal	2	1	0
C-29	M	150	Moderate and small; budding	Cuboidal	1	2	1
C-31	M	130	Large size	Flat	3	0	0
C-32	M	140	Small and irregular; solid areas	High cuboidal	1	3	2
C-33	F	120	Moderate, small and irregular	Cuboidal	1	3	1
C-34	F	135	Small and irregular	High cuboidal	1	3	2
C-35	F	115	Small size	High cuboidal	2	2	1
C-36	F	140	Moderate and irregular	Cuboidal	1	1	0
C-37	M	120	Small, moderate, irregular; solid areas	High cuboidal	1	2	2
C-38	F	102	Small, moderate, irregular; solid areas	High cuboidal; budding	1	2	2
C-39	M	150	Moderate, irregular; tubes, solid areas	High cuboidal	1	2	2
C-40	F	125	Moderate, small and irregular	High cuboidal	1	1	2
C-41	F	130	Large and moderate size	Cuboidal	2	2	0
C-42	F	125	Moderate; budding	Cuboidal	2	2	1
C-43	F	175	Moderate size	Cuboidal	2	2	1
C-44	F	135	Moderate and irregular size	High cuboidal	1	3	2
C-45	F	130	Moderate and irregular size	High cuboidal	1	3	2

TABLE 7.—*Group D, Diet Low in Iodine and High in Calcium Lactate*

Rat No.	Sex	Weight, Gm.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
D- 1	M	98	Large and moderate size	Flat	3	0	0
D- 2	M	96	Large and moderate size	Flat	3	0	0
D- 3	M	140	Moderate; small tube forms, few solid areas	Flat and low cuboidal	2	2	1
D- 4	M	200	Moderate and large size	Flat and low cuboidal	2	1	1
D- 5	M	113	Large and moderate size	Flat	3	0	0
D- 6	M	140	Large and moderate size	Flat	3	0	0
D- 7	M	170	Large and moderate size	Flat	3	0	0
D- 8	M	150	Large and moderate size	Flat	3	0	0
D- 9	M	180	Large and moderate size	Flat	3	0	0
D-10	M	190	Moderate; few solid areas	Flat and low cuboidal	3	1	0
D-11	F	185	Large and moderate size	Flat	3	0	0
D-12	F	180	Large and moderate size	Flat	3	0	0
D-13	F	138	Large and moderate size	Flat	3	0	0
D-14	F	165	Moderate size	Flat and low cuboidal	3	1	0
D-15	F	140	Large and moderate size	Flat	3	0	0
D-16	M	210	Large and moderate size	Flat	3	0	0
D-17	F	210	Large and moderate size	Flat	3	0	0
D-18	F	160	Large and moderate size	Flat	3	0	0
D-19	F	210	Moderate size	Low cuboidal	3	1	0
D-20	F	160	Moderate size	Flat and low cuboidal	3	1	1

COMMENT

This experimental study agrees with the work of Hellwig [1] and the views of Wegelin [8] that thyroid hyperplasia is not due to a deficiency of iodine alone. McCarrison's [13] views that thyroid changes occur in animals when fed on a diet deficient in vitamins and leafy vegetables are not borne out. The study substantiates Hellwig's point of view that a positive factor is the essential cause, and when combined with a low iodine content may produce goiter. The experiments coincide with his results in that calcium chloride may act as a positive agent in producing goiter. Although there were definite changes in the thyroid glands in animals fed on a diet high in sodium chloride and low in

TABLE 8.—*Group E, Diet Low in Iodine and High in Sodium Chloride*

Rat No.	Sex	Weight, Gm.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
E- 2	F	130	Small; tubes, solid areas, buds	Columnar and cuboidal	1	2	3
E- 3	M	140	Small; tubes, solid areas	High cuboidal	1	3	3
E- 4	F	150	Small; tubes, solid areas	High cuboidal	1	3	3
E- 5	F	130	Small; tubes, solid areas	High cuboidal	1	3	3
E- 6	F	120	Small; tubes, solid areas	Cuboidal	1	3	2
E- 7	M	132	Small; tubes, solid areas	High cuboidal and columnar	1	0	3
E- 9	F	125	Small; tubes, solid areas	High cuboidal	1	2	2
E-10	M	123	Small; tubes, solid areas	High cuboidal	1	2	3
E-11	M	128	Small; tubes, solid areas	High cuboidal	1	1	3
E-12	F	110	Moderate size	Flat	3	0	0
E-13	M	140	Small; tubes, solid areas	High cuboidal	1	1	3
E-14	F	200	Moderate size	Cuboidal	2	1	1
E-15	M	135	Moderate, small; solid areas	Cuboidal	1	0	2
E-16	M	130	Small; tubes, solid areas	High cuboidal	1	0	3
E-17	M	120	Small size; tubes	Cuboidal	1	1	2
E-18	M	145	Moderate, small; tubes, solid areas	High cuboidal	2	1	3

iodine and none in those fed on a diet high in calcium lactate and low in iodine, the conclusions are not absolutely clear. The data would rather indicate that the positive element in this series of experiments was the chlorine and not the calcium ion. Whether this action is specific for chlorine or may occur with other halogens is not absolutely proved in this study. Further investigation, including verification of this work in a larger series, a series in which another calcium ingredient is used, and other halogens employed, is to be done and reported on later.

SUMMARY

White rats fed on a diet low in iodine in a relatively nonendemic region failed to have thyroid hyperplasia.

Changes in the thyroid gland did not occur in rats fed on a diet poor in vitamins and leafy vegetables.

13. McCarrison, R.: A Goiter Survey in Albino Rats, Brit. M. J. **2**:989 (May 31) 1930.

A 2 per cent solution of calcium chloride, combined with a diet low in iodine, produced a definite thyroid hyperplasia in a large percentage of the experimental animals.

Hyperplasia was not observed in experimental rats fed on a diet high in calcium lactate and low in iodine.

Definite changes in the thyroid gland, similar to those obtained by a diet high in calcium chloride and low in iodine, were found in rats fed on a diet high in sodium chloride and low in iodine. This suggests that chlorine (or the halogens as a group) may act as a positive factor in the production of thyroid hyperplasia.

EFFECT OF INSULIN AND DEXTROSE ON THE NORMAL AND ON THE OBSTRUCTED INTESTINE

I. M. GAGE, M.D.

ALTON OCHSNER, M.D.

AND

R. A. CUTTING, M.D.

NEW ORLEANS

The intravenous administration of dextrose solution has become popular both as a preoperative and as a postoperative therapeutic measure. In addition to supplying the body with the necessary fluids in cases of dehydration, dextrose solution also supplies food that is readily utilized. A hypertonic solution of dextrose is an excellent diuretic, and therefore is of value in the prevention and treatment of cerebral edema. Dextrose solution is useful in the treatment of shock, and by virtue of its caloric value it tends to prevent and combat the development of acidosis. Largely owing to the work of Thalhimer,[1] the combination of dextrose and insulin in the treatment of nondiabetic acidosis became popular. The use of this combination was continued for a considerable period of time, but within recent years it is the tendency among most clinicians not to use insulin but to administer dextrose alone. Dextrose is usually employed in 5 or 10 per cent dilutions, unless a dehydrating or diuretic effect is desired. The use of the continuous dextrose infusion ("intravenous drip"), as suggested by Matas,[2] is popular and frequently life-saving.

Bulatoa and Carlson,[3] in 1924, showed that the intravenous injection of from 5 to 10 Gm. of dextrose in 50 per cent solution produced an inhibition of the movement of the stomach that lasted from 10 to 60 minutes. Equimolar solutions of sodium chloride and the same amounts of 50 per cent lactose solution had no effect on gastric activity. The injection of from 20 to 40 units of insulin produced a marked increase in gastric

From the Department of Surgery, Tulane University School of Medicine.

1. Thalhimer, W.: Insulin Treatment of Postoperative (Nondiabetic) Acidosis, J. A. M. A. **81**:383 (Aug. 4) 1923.

2. Matas, Rudolph: Continued Intravenous Drip, Ann. Surg. **79**:643 (May) 1924.

3. Bulatoa, E., and Carlson, A. J.: Contributions to the Physiology of the Stomach: Influence of Experimental Changes in Blood Sugar Level on Gastric Hunger Contractions, Am. J. Physiol. **69**:107, 1924.

activity. These same observers found that the intravenous injection of 5, 10 or 20 Gm. of dextrose in a diabetic dog following complete pancreatectomy did not produce typical prolonged hunger contractions. Bulatoa and Carlson [3] believe that these changes following the administration of dextrose and insulin are due to a change in the energy metabolism of the gastric motor tissue as a result of the available glycogen being reduced. Stucky, Rose and Cowgill [4] determined the effect of dextrose and insulin on the stomach in the presence of vitamin B deficiency. Five of the seven animals with vitamin B deficiency showed evidence of decreased gastric motility. Of sixteen experiments, four (25 per cent) showed that the injection of insulin was followed by an increase in gastric motility. In twelve (75 per cent), insulin produced no significant change in the motility of the empty stomach. Stucky and his co-workers concluded from this investigation that the disturbances in gastric motility resulting from vitamin B deficiency are not the result of hypoglycemia, and that the hypoglycemia produced by the administration of insulin in vitamin B-deficient animals does not alter gastric motility. They believe that in the 25 per cent of the cases in which increased gastric motility followed the administration of insulin the action was due to the insulin itself and not to vitamin B, as insulin contains no vitamin B. There was no relationship between the level of the blood sugar and the gastric motility. Quigley, Johnson and Solomon [5] showed in man, by placing balloons in different parts of the stomach, that the response to insulin and dextrose was qualitatively the same in all parts of the stomach. They found that characteristically the injection of insulin produced prolonged gastric activity associated with a marked and sustained increase in gastric tone. The administration of dextrose into the stomach did not produce the characteristic inhibition of gastric activity, whereas the gastric response following the intraduodenal administration of dextrose corresponded to that which followed the intravenous administration. Templeton and Quigley [6] determined the effect of dextrose and insulin on a Heidenhain pouch of the stomach. In contrast to the normal stomach, the Heidenhain pouch showed inhibition of motility and decrease of tone. This in some few cases lasted for as long as 4 hours. In those instances in which concomitant tracings were

4. Stucky, C. J.; Rose, W. B., and Cowgill, G. R.: Studies in the Physiology of Vitamins: VI. Effect of Insulin on Gastric Motility in Vitamin B Deficiency, Am. J. Physiol. **87**:85, 1928.

5. Quigley, J. P.; Johnson, V., and Solomon, E. I.: Effect of Insulin on the Motility of the Gastro-Intestinal Tract: Action on the Stomach of Normal Fasting Man, Am. J. Physiol. **90**:89, 1929.

6. Templeton, R. D., and Quigley, J. P.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: II. Action on the Heidenhain Pouch, Am. J. Physiol. **91**:467, 1930.

made of the pouch and the normal stomach, inhibition in the pouch occurred simultaneously with increased motility of the stomach. The intravenous administration of dextrose to the fasting animal with a Heidenhain pouch produced no change in activity of the pouch, but concomitant tracings of the stomach proper showed the characteristic inhibition. Templeton and Quigley [6] believe that the reaction produced by dextrose and insulin in a Heidenhain pouch differs from that in the stomach proper because in the former the nerve fibers from the vagi have been divided and probably disturbances in the plexuses of Meissner and Auerbach have occurred. They also suggested that the fundic portion of the stomach from which the pouch was made differs qualitatively from the pyloric portion. Quigley and Templeton [7] determined the effect of insulin and dextrose on a pyloric pouch and on the stomach proper following double splanchnicotomy. They found that before splanchnicotomy subcutaneous and intravenous injection of insulin did not modify the motility or the tone of the pyloric pouch. Similar negative results were obtained following the intravenous injection of dextrose, irrespective of whether the dextrose followed or preceded the insulin or was given alone. After double splanchnicotomy, it was found that there was a characteristic increase in gastric motility as described by Carlson. This increase was augmented by the subcutaneous injection of 20 units of insulin. The intravenous administration of dextrose produced a temporary decrease in gastric motility, whereas the administration of dextrose without an antecedent injection of insulin produced complete inhibition of gastric activity. The increased gastric activity was apparently slightly greater in the splanchnicotomized animals than in the normal animals. These same investigators [8] determined the reaction of the stomach to dextrose and insulin after vagotomy. All the animals showed the type of hunger contractions following vagotomy described by Carlson. As a rule, the injection of insulin, in contrast to the normal, produced an inhibition in gastric motility in the vagotomized animal, the inhibition lasting several hours. Quigley and Templeton [8] concluded from this that insulin apparently acts centrally, the impulses being carried over the vagi, and that following vagotomy impulses cannot be carried to the stomach. They agreed with Bulatoa and Carlson [3] that the gastric response to dextrose and insulin is not due to the dextrose and insulin per se, but is due to the changes in blood sugar and to the modified cell metabolism which are produced by the insulin and the

7. Quigley, J. P., and Templeton, R. D.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: III. A. Action on the Pyloric Pouch. B. Action on the Stomach Following Double Splanchnicotomy, Am. J. Physiol. **91**:475, 1930.

8. Quigley, J. P., and Templeton, R. D.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: IV. Action on the Stomach Following Double Vagotomy, Am. J. Physiol. **91**:482 (Jan.) 1930.

dextrose. The inhibiting effect that is exerted by the intravenous injection of dextrose on the stomach occurs probably through the vagi, for it is absent in the Heidenhain pouch and in the stomach after vagotomy. The assumption that the stimulating influences reaching the stomach after the injection of insulin pass by way of the vagi is substantiated by the investigations of Wilder and Schlutz.[9] They found that the administration of atropine to an animal with gastric hyperactivity produced by insulin caused marked inhibition (often complete cessation) of gastric motility and loss in tone. This was associated with a lowering of the blood sugar. They believe that the stimulating effect of insulin on the stomach is due to hyperirritability of the vagi. Quigley and Solomon [10] in determining the effect of insulin and dextrose on the human stomach found that following the subcutaneous administration of insulin increased duodenal and gastric activity occurred. The increase in duodenal activity, which usually occurred about 15 minutes before the gastric activity became marked, consisted largely of an increase in the frequency of the contraction with little change in the tone. At the time that the gastric movements began, they became more frequent than those in the duodenum. The administration of atropine, and also of a dextrose solution by mouth, completely stopped the movements in the duodenum and stomach. Quigley and Solomon [10] also found, by introducing balloons through an appendectomy wound in animals, that following the administration of insulin there was an increase in colonic movement. The stimulation occurred more uniformly in the colon than in the stomach. The administration of dextrose caused complete cessation of colonic movement, which, however, was less complete than that seen in the stomach. Quigley and Barnes,[11] determining the effect of pituitary extract and insulin on the stomach, found that pituitary preparations invariably produced diminution in gastric activity. Associated with this was a slight rise in blood sugar, which, however, was not sufficient to account for the diminished gastric activity. The administration of pituitary preparations to insulinized animals produced a similar inhibition in the motility of the stomach. Relatively recently, Quigley and Hallaran [12] concluded from their investigations that the spontaneous

9. Wilder, R. L., and Schlutz, F. W.: Action of Atropine and Adrenaline on Gastric Tonus and Hypermotility Induced by Insulin Hypoglycemia, Am. J. Physiol. **96**:54, 1931.

10. Quigley, J. P., and Solomon, E. I.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: V. A. Action on the Human Duodenum. B. Action on the Colon of Dogs, Am. J. Physiol. **91**:488 (Jan.) 1930.

11. Quigley, J. P., and Barnes, B. O.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: VI. Antagonistic Action of Posterior Pituitary Lobe Preparations, Am. J. Physiol. **95**:7, 1930.

12. Quigley, J. P., and Hallaran, W. R.: The Independence of Spontaneous Gastro-Intestinal Motility and Blood Sugar Levels, Am. J. Physiol. **100**:102, 1932.

motility of the stomach and intestine is unaffected by the intravenous injection of dextrose solution, whereas the increased activity produced by insulin is inhibited. They feel that the changes occurring in the motility of the stomach and intestine following the intravenous injection of dextrose solutions are inconsequential.

Because of the alterations in motility of the normal stomach and duodenum of man and animals and the normal intestine of animals produced by the administration of dextrose and insulin, and because dextrose solutions are so universally employed clinically, especially in the "poor risk" patient (including those with ileus), it was considered advisable to determine the effect which these substances exert on the normal and on the obstructed small intestine.

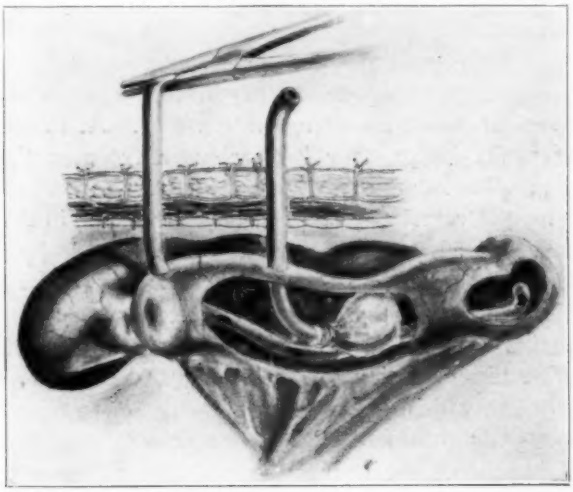

Fig. 1.—Drawing illustrating the relative arrangement of the enterostomy tube and the tube carrying the balloon used to record intestinal movement. As illustrated, the terminal ileum has been divided and the two ends inverted. A fenestrated enterostomy tube is introduced into the distal end of the proximal portion of the ileum and allowed to extend proximally in the intestine for approximately 20 cm. About 5 cm. proximal to this a rubber tube carrying a balloon is introduced proximally into the intestine but not extending beyond the end of the enterostomy tube. As long as the enterostomy tube is open, an obstruction is not present. However, an obstruction may be produced by clamping, as illustrated in the diagram, or by tying the tube.

Ninety-two observations were made on thirty dogs, twenty-two on the normal animal, thirteen on animals with 24 hour obstruction, twenty-two on animals with 48 hour obstruction, twenty-five on animals with 72 hour obstruction, and ten on animals with 96 hour obstruction. The effect on intestinal activity of insulin alone was determined seventeen

times; of dextrose alone, sixteen times; of dextrose and insulin combined, ten times; of insulin preceded by dextrose, ten times, and of dextrose preceded by insulin, thirty-nine times. All observations were made on unanesthetized animals. This and repeated observations on the same animal were made possible by employing the following technic.[13]

TECHNIC

Under aseptic precautions, the terminal ileum was divided and each end inverted by a purse string suture. About 5 cm. proximal to the inverted end of the proximal portion, a fenestrated tube was introduced through an enterostomy opening and allowed to extend proximally in the lumen of the bowel for about 21 cm. About 5 cm. proximal to this, a second tube carrying a balloon was introduced through another enterostomy opening, the end carrying the balloon being directed proximally, but so placed that the fenestrated enterostomy tube extended beyond the balloon (fig. 1). Both tubes were brought out through the omentum, and the abdominal wall was closed in layers. The animal was allowed to recover completely, and after 24 hours the tube carrying the balloon was connected with a

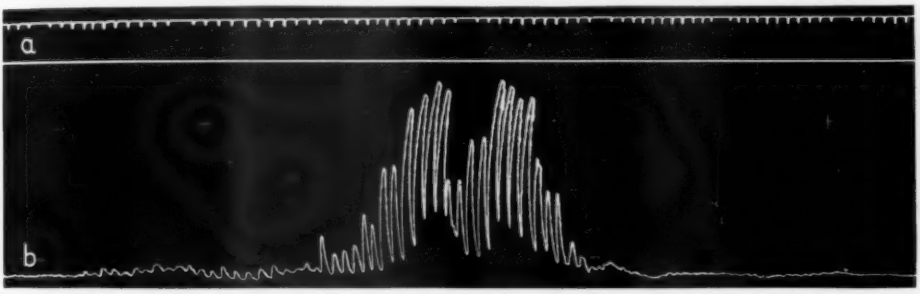

Fig. 2.—Kymographic tracing showing the effect of insulin on the activity of the normal intestine. Time is indicated by *a* (in all the figures the time interval between the small vertical bars is one-tenth minute, or six seconds). Tone and movement of the ileum are indicated by *b*. The tracing was taken 40 minutes after the administration of insulin. There was not only an increase in tone, but also a marked increase in amplitude of intestinal movement.

Marey tambour, and kymographic tracings were obtained. Concomitant respiratory tracings were made. Observations were made on the normal unanesthetized animal, following which the enterostomy tube was clamped, producing a mechanical obstruction. Observations were made daily as long as the animal survived. Blood sugar determinations were made before the beginning of the experiment and at intervals subsequently, an attempt being made to obtain a specimen at the height of the intestinal activity. Blood sugar determinations were made by Folin-Wu technic.

The doses of insulin and dextrose varied in different experiments, but in each instance the dextrose was given intravenously as a 10 per cent solution; the

13. Gage, I. M.; Ochsner, Alton, and Cutting, R. A.: Effect of Insulin and Glucose on Normal and Obstructed Intestine, Proc. Soc. Exper. Biol. & Med. **29**: 264, 1931.

amounts were usually between 6 and 10 Gm., with an average of 7.5 Gm. Large doses of insulin were used and were given intravenously; the dose varied between 20 and 40 units. In only four instances were there hypoglycemic manifestations. It was found that the average period of time before changes in the intestinal activity occurred after the intravenous injection of insulin was 30 minutes, whereas the changes that followed the intravenous administration of dextrose occurred usually within a few minutes.

The results are based on an analysis of the kymographic tracings.

EFFECT OF INSULIN ALONE ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—One observation was made on the normal intestine 30 minutes after the intravenous administration of 40 units of insulin. There was a decrease in blood sugar from 159 to 151 mg. per hundred cubic centimeters (5 per cent decrease). The intestinal tone and amplitude were increased 30 and 16 mm., respectively (fig. 2). The increased activity lasted 6 minutes.

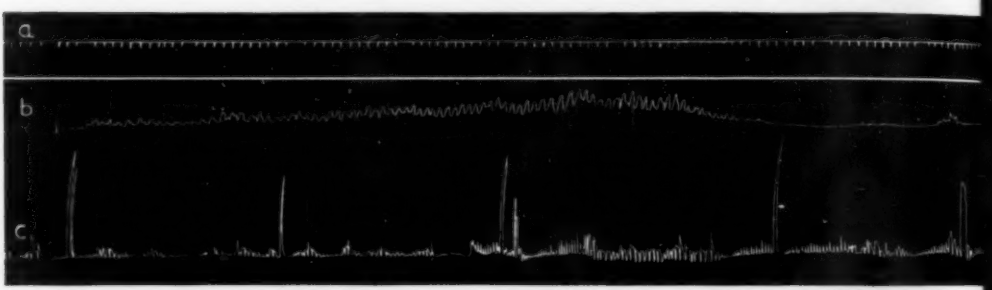

Fig. 3.—Kymographic tracing showing the effect of insulin on an intestine that had been obstructed for 24 hours. Time is indicated by *a*, tone and movement of the ileum by *b*, and respiration by *c*. The tracing was taken 34 minutes after the administration of insulin. The increase in tone was not especially marked, but the increase in intestinal movement was very definite.

Twenty-Four Hour Obstruction.—One observation was made. After the administration of 20 units of insulin, there was a decrease in blood sugar from 107 to 61 mg. per hundred cubic centimeters (43 per cent decrease). There was an increase in intestinal tone and amplitude of 4 and 18 mm., respectively (fig. 3). The duration of this increased activity was 2 minutes.

Forty-Eight Hour Obstruction.—Five observations were made. In each instance, 40 units of insulin was used, and in every case a decrease in blood sugar occurred, from a normal average of 119 mg. to 74 mg. per hundred cubic centimeters (37 per cent decrease). The observations were made between 30 and 40 minutes after the administration of insulin with one exception in which the interval was 58 minutes. In only two instances was there an increase in intestinal activity, the average increase in tone and amplitude being 10 and 1.5 mm., respectively. The average length of time of increased intestinal activity was 12 minutes. In the instances in which increased activity occurred, the blood sugar was decreased from an average normal of 159 mg. to 103 mg. per hundred cubic centimeters (29 per cent decrease), whereas in those instances in which no change occurred,

the blood sugar decreased from an average normal of 93 mg. to 55 mg. (42 per cent decrease). In three observations (60 per cent), there was no change in the activity of the intestine.

Seventy-Two Hour Obstruction.—Seven observations were made. Forty units of insulin was given in six instances and 10 units in one. In each instance there was a decrease in blood sugar from an average blood sugar value of 105 mg. to 72 mg. per hundred cubic centimeters (22 per cent decrease). The observations

TABLE 1.—*Effect of Insulin Alone on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 1.....	100% T 30; A 16; T′ 6 B 159; B′ 151; —5%	.....	.....	.....	100% B 159; B′ 151; —5%
24 hr. obstruction; 1....	100% T 4; A 18; T′ 2 B 107; B′ 61; —43%	.....	.....	.....	100% B 107; B′ 61; —40%
48 hr. obstruction; 5....	40% T 10; A 1.5; T′ 12 B 159; B′ 103; —29%	60% B 93; B′ 55; —42%	.....	.....	100% B 119; B′ 74; —37%
72 hr. obstruction; 7....	43% T 4; A 25; T′ 6 B 123; B′ 77; —37%	43% B 82; B′ 57; —30%	14% T 10; A 0; T′ 37 B 112; B′ 62; —44%	.....	100% B 105; B′ 72; —22%
96 hr. obstruction; 3....	66% T 7; A 3.5; T′ 5.5 B 113; B′ 49; —56%	33% B 115; B′ 93; —19%	.....	.....	100% B 114; B′ 64; —44%

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (E′) is expressed in minutes. The average blood sugar values before (B) and after (B′) the administration of insulin are given in milligrams, with the percentage of loss.

were made at varying periods of time after the administration of insulin. All with the exception of one (which was made after 11 minutes) were made between 30 and 40 minutes after the administration of insulin. In three instances there was an increase in intestinal activity, the average increase in tone and amplitude being 4 and 25 mm., respectively. The average duration of the increased activity was 6 minutes. In three instances there was no change, and in one there was an actual decrease in activity of the intestine. In the one instance in which a decrease in activity occurred, there was a fall in tone of 10 mm., which persisted for 37 minutes. The average blood sugar values before the administration of insulin in the

instances in which there was an increase, no change or a decrease in intestinal activity were 123, 83 and 112 mg. per hundred cubic centimeters, respectively. The average blood sugar values after the administration of insulin for the same groups were 77, 57 and 62 mg. per hundred cubic centimeters, respectively.

Ninety-Six Hour Obstruction.—Three observations were made. Forty units of insulin was administered intravenously in each instance. Observations were made 25, 37 and 58 minutes, respectively, after the administration of insulin. In one instance, the blood sugar determinations for technical reasons were unreliable and were, therefore, discarded. In the other two there was a definite decrease in blood sugar from a normal average of 114 mg. to 64 mg. per hundred cubic centimeters. An increase in intestinal activity occurred in two instances, an average increase in tone and amplitude of 7 and 3.5 mm., respectively. The average duration of the increased activity was 5.5 minutes. In one of the three animals, no change in intestinal activity occurred.

EFFECT OF DEXTROSE ALONE ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Seven observations were made. In each instance, 75 cc. of 10 per cent dextrose solution was administered intravenously. In two animals, the

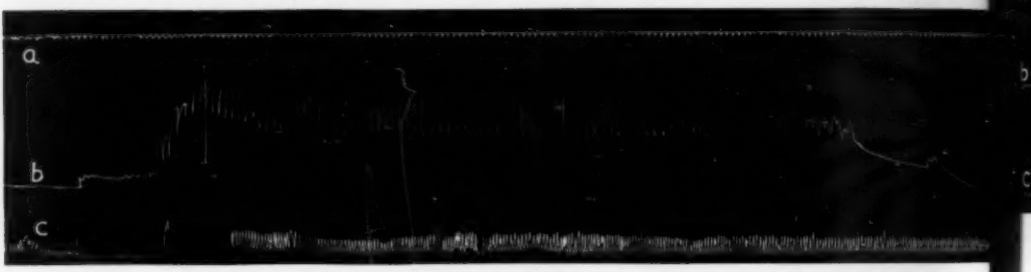

Fig. 4.—Kymographic tracing showing the inhibiting effect of dextrose on a normal intestine that had been made hyperactive by means of splanchnic analgesia. Time is indicated by *a*, tone and movement of the ileum by *b*, and respiration by *c*. At the extreme left, following splanchnic analgesia, there occurred a marked increase in intestinal activity as evidenced by the increase in tone and amplitude of intestinal movement. At about the midportion of the kymographic tracing an infusion of 10 per cent dextrose was started and continued approximately 5.5 minutes, at which time 75 cc. had been administered. Within 1 minute after the completion of the infusion, as shown in the right hand portion of the tracing, there was a rapid fall in intestinal tone with almost complete absence of movement. The tone assumed a lower level than that before the splanchnic analgesia.

dextrose was administered without any previous procedures having been used. In five, hyperperistalsis had been produced by means of either intravenous injection of hypertonic salt solutions or splanchnic block (fig. 4). Following the administration of dextrose there was in each instance a definite decrease in intestinal activity, the average decreases in tone and amplitude being 27.2 and 10.6 mm., respectively (fig. 4). The average duration of this inhibition was over 13 minutes.

In five instances in which blood sugar determinations were made at such times that they could be correlated with the intestinal movement, there occurred a marked increase from an average normal of 148 mg. to 298 mg. per hundred cubic centi-

meters of blood (101 per cent increase). The percentage increases in blood sugar varied from 37 to 171 per cent.

Twenty-Four Hour Obstruction.—Three observations were made. In each instance, peristalsis had been induced by intravenous injection of hypertonic salt solutions; the dextrose was administered at the height of the intestinal activity (fig. 5). The interval of time between the administration of dextrose and the first effect on the intestine varied from 2 to 9 minutes. Seventy-five cubic centimeters of 10 per cent solution was employed in each instance. The blood sugar was increased in two of the three observations from a normal average of 119 mg. to 202 mg. per hundred cubic centimeters of blood. The intestinal movement was decreased in each instance, there being average decreases in tone and amplitude of 38 and 5 mm., respectively. This inhibition persisted for an average of 19 minutes.

Forty-Eight Hour Obstruction.—Four observations were made. In one instance, dextrose was given alone without any previous medication; in the remaining three, hypertonic chloride solutions had been employed to stimulate the intestine. Seventy-five cubic centimeters of 10 per cent dextrose solution was used in each instance.

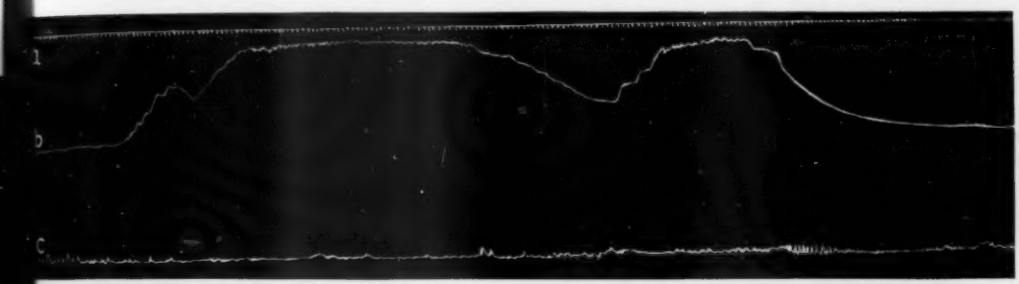

Fig. 5.—Kymographic tracing showing the inhibiting effect of dextrose solution on an intestine which had been obstructed for 24 hours and which had been made hyperactive by an intravenous administration of hypertonic salt solution. Time, tone and movement of the ileum, and respiration are represented by *a*, *b* and *c*. As shown on the left of the tracing, there was an increase principally in intestinal tone, but also some increase in intestinal movement, following the intravenous administration of 10 cc. of 20 per cent salt solution. Just to the right of the mid-portion of the tracing an infusion of 10 per cent dextrose was begun. Within 2 minutes after the start of the infusion there was a cessation of all intestinal movement with rapid loss in intestinal tone.

The blood sugar was increased in each instance from a normal average of 121 mg. to 282 mg. per hundred cubic centimeters of blood (133 per cent increase). The individual percentage increases in blood sugar varied from 128 to 224. In every instance, there was an inhibition of the intestinal activity, there being average decreases in tone and amplitude of 15 and 5 mm., respectively. The average duration of this inhibition was more than 6 minutes.

Seventy-Two Hour Obstruction.—Two observations were made. In each instance, the intestine had been activated by a previous administration of hypertonic salt solution. Seventy-five cubic centimeters of 10 per cent dextrose was injected intravenously. The average interval of time between the infusion and the effect produced on the intestine was 15 minutes. There occurred a marked increase in

blood sugar in each instance from an average normal of 97 mg. to 231 mg. per hundred cubic centimeters of blood (141 per cent average increase). There was a decrease in intestinal tone and amplitude in both instances. The activity of the intestine was definitely decreased in each instance, the average decreases in tone and amplitude of movement being 10 and 10 mm., respectively. The average duration of the inhibition was 10 minutes.

EFFECT OF INSULIN AND DEXTROSE COMBINED ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Three observations were made. In two instances, 75 cc., and in one, 60 cc. of a 10 per cent dextrose solution was administered. In two

TABLE 2.—*Effect of Dextrose Alone on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 7.....	.....	.....	100% T 27.2; A 10.6; T′ 13+ B 148; B′ 298; +101%	100% B 148; B′ 298; +101%	.....
24 hr. obstruction; 3....	.....	.....	100% T 38; A 5; T′ 19 B 163; B′ 184; +12%	66.6% B 119; B′ 202; +69%	33.3% B 250; B′ 149; —40% B 163; B′ 184; +12%
48 hr. obstruction; 4....	.....	.....	100% T 15; A 5; T′ 6 B 121; B′ 282; +133%	100% B 121; B′ 282; +133%	.....
72 hr. obstruction; 2....	.....	.....	100% T 10; A 10; T′ 10 B 97; B′ 231; +141%	100% B 97; B′ 231; +141%	.....

The number of dogs in which there was an increase, no change or a decrease is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is expressed in minutes. The average blood sugar values before (B) and after (B′) the administration of dextrose are given in milligrams, with the percentage of gain or loss.

instances, 40 units, and in one, 20 units, of insulin was given. Blood sugar determinations were made 38 minutes after the intravenous infusion. In two instances, the blood sugar was increased from a normal average of 81 mg. to 102 mg. per hundred cubic centimeters of blood (26 per cent increase) whereas in one the blood sugar was decreased from a normal value of 106 mg. to 73 mg. per hundred cubic centimeters. In only one instance was there a slight increase in intestinal activity as evidenced by an increase in amplitude of movement of 1 mm., which persisted. In two instances, no change occurred in the intestinal activity.

Twenty-Four Hour Obstruction.—Three observations were made. In each instance, 75 cc. of 10 per cent dextrose solution and 40 units of insulin were used.

The time elapsing between the administration of the solution and the appearance of intestinal activity varied from 54 to 57 minutes. The blood sugar was decreased in each instance from an average normal value of 136 mg. to 75 mg. per hundred cubic centimeters of blood (159 per cent decrease). There was an increase in intestinal tone of 5 mm. in one instance, a decrease in tone of 9 mm. in another, and in a third the intestinal activity was not changed. The normal blood sugar value, i. e., before the administration of dextrose and insulin, was higher (167 mg.) in the animal in which increased activity of the intestine occurred than that (106 mg.) in the animal in which there resulted no change in activity.

TABLE 3.—*Effect of Dextrose and Insulin Combined on Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood Sugar	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 3.....	33.3% T 0; A 1; T′ cont. B 97; B′ 107; +15%	66.6% B 87; B′ 85; −2%	.....	66.6% B 81; B′ 102; +26% B 89; B′ 93; +18%	33% B 106; B′ 73; −31%
24 hr. obstruction; 3....	33.3% T 5; A 0 B 167; B′ 77; −31%	33.3% B 106; B′ 73; −31%	33.3% T 9; A 0	.....	100% B 136; B′ 75; −59%
48 hr. obstruction; 3....	33.3% T 0; A 5; T′ 6 B 100; B′ 71; −29%	66.6% B 87; B′ 57; −34%	.....	.....	100% B 94; B′ 64; −32%
72 hr. obstruction; 1....	100% T 27; A 12; T′ 16 B 97; B′ 79; −18%	.....	.....	.....	100% B 97; B′ 79; −18%

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is expressed in minutes. The average blood sugar values before (B) and after (B′) the combined administration of dextrose and insulin are given in milligrams with the percentage of gain or loss.

Forty-Eight Hour Obstruction.—Three observations were made. In two instances, 75 cc., and in one, 80 cc. of 10 per cent dextrose solution was introduced intravenously. In each instance, the amount of insulin combined with the dextrose was 40 units. Intestinal activity became evident between 30 and 35 minutes after the intravenous administration of the dextrose and insulin. The blood sugar decreased in each instance from an average normal value of 94 mg. to 64 mg. per hundred cubic centimeters of blood (32 per cent decrease). In two instances, no change in intestinal activity occurred. In one, however, there was an increase in amplitude of movement of 5 mm. without a concomitant rise in tone, which persisted approximately 6 minutes. The preliminary blood sugar value in the animal in which increased intestinal activity followed the injection of dextrose and

insulin was 100 mg. per hundred cubic centimeters as compared with the average blood sugar value of 87 mg. in the two animals in which no intestinal response occurred.

Seventy-Two Hour Obstruction.—One observation was made. Seventy-five cubic centimeters of 10 per cent dextrose solution and 10 units of insulin were given intravenously. The stimulating effect on the intestine was noted 18 minutes after the administration. The blood sugar was decreased from 97 to 79 mg. per hundred cubic centimeters of blood. The effect on the intestine was marked, in that the intestinal tone and amplitude were increased 27 and 12 mm., respectively, which effect persisted approximately 16 minutes (fig. 6).

Fig. 6.—Kymographic tracing showing the effect of dextrose solution and insulin combined on the 72 hour-obstructed intestine. There are three definite periods of increased intestinal activity, each consisting of an increase in tone and intestinal movement. These periodic increases in intestinal activity correspond to the cramplike pain experienced by human beings.

Fig. 7.—Kymographic tracing showing the effect on the normal intestine of the administration of insulin which had been preceded by an intravenous infusion of dextrose. Time, tone and movement of ileum, and respiration are represented by *a*, *b* and *c*. As illustrated in the left part of the tracing, the infusion of dextrose caused a cessation of intestinal movement. Nine minutes after completion of the dextrose infusion, insulin was administered, and 7 minutes later, as shown in the right portion of the tracing, there was a definite increase in intestinal tone and also in intestinal movement.

EFFECT OF INSULIN PRECEDED BY DEXTROSE ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Two observations were made. In each instance, the animal had received not only dextrose prior to the administration of the insulin, but a combination of dextrose and insulin. In one, subsequent to the initial infusion with dextrose and insulin, the animal had received two injections each of 75 cc. of 10 per cent dextrose solution before the insulin was given. Increased intestinal

activity occurred 7 minutes and 25 minutes, respectively, after the injection of 40 units of insulin (fig. 7). In each instance, there was a decrease in blood sugar from an average normal value of 193 mg. to 139 mg. per hundred cubic centimeters of blood (25 per cent decrease). In one instance, there was no effect on the intestinal activity; in the other, however, 7 minutes after the intravenous administration of insulin, there was a definite increase in activity as evidenced by an increase in tone and amplitude of 39 and 3 mm., respectively, which persisted 6 minutes.

TABLE 4.—*Effect of Insulin Preceded by Dextrose on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood Sugar	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 2.....	50% T 39; A 3; T′ 6 B 288; B′ 210; —27%	50% B 98; B′ 69; —29%	.....	.....	100% B 193; B′ 139; —25%
24 hr. obstruction; 1....	100% T 20; A 2; T′ 2	.....	.....	.....	.....
48 hr. obstruction; 2....	100% T 13; A 4; T′ 12+++ B 207; B′ 105; —49%	.....	.....	.....	100% B 207; B′ 105; —49%
72 hr. obstruction; 3....	66% T 2.5; A 3.5; T′ 8 B 204; B′ 48; —54%	33% B 182; B′ 43; —76%	.....	.....	100% B 130; B′ 46; —64%
96 hr. obstruction; 2....	50% T 3; A 2; T′ 8 B 214; B′ 96; —55%	50% B 205; B′ 79; —61%	.....	.....	100% B 209; B′ 87; —58%

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increase in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is expressed in minutes. The average blood sugar values before (B) and after (B′) the administration of insulin preceded by dextrose are given in milligrams, with the percentage of loss or gain.

Twenty-Four Hour Obstruction.—One observation was made. Twenty units of insulin was given 9 minutes after an intravenous injection of 75 cc. of 10 per cent dextrose solution. An increase in intestinal activity occurred 10 minutes after the administration of insulin. No blood sugar determinations were made. There was an increase in intestinal activity. The intestinal tone and amplitude were increased 20 and 2 mm., respectively, which activity lasted 2 minutes.

Forty-Eight Hour Obstruction.—Two observations were made. In one instance in which 50 cc. of 10 per cent dextrose solution was given 6 minutes before 40

units of insulin, increased intestinal activity was noted 28 minutes after the administration of insulin. In the other in which an injection of 50 cc. of 10 per cent dextrose preceded the administration of insulin by 24 minutes, activity occurred 6 minutes after the injection of insulin. In each instance, there was a decrease in blood sugar from a normal value of 207 mg. to 105 mg. per hundred cubic centimeters (49 per cent decrease). The intestine was definitely stimulated in each case, there being average rises in tone and amplitude of 13 and 4 mm., respectively, which effect persisted in one for 8 minutes until another infusion of dextrose was made, and in the other for longer than 20 minutes (fig. 8).

Seventy-Two Hour Obstruction.—Three observations were made. In each instance prior to the administration of dextrose that preceded the administration of insulin, a previous administration of insulin had been given. The intestinal effect occurred, on an average, 12 minutes after the intravenous administration of 40 units of insulin in two cases and 20 units in one case. In each instance, there was a decrease in blood sugar from a normal average value of 130 mg. to 46 mg. per hundred cubic centimeters of blood (64 per cent decrease). In one instance there was no change in intestinal activity. In two there occurred a stimulation of

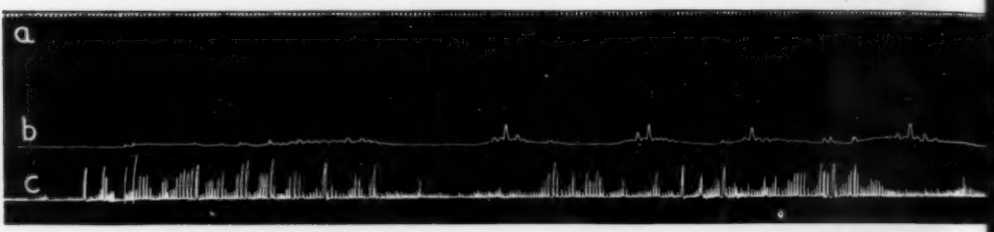

Fig. 8.—Kymographic tracing showing the effect of an administration of insulin preceded by an intravenous infusion of dextrose on an intestine that had been obstructed for 48 hours. Time, tone and movement of the ileum, and respiration are represented by *a*, *b* and *c*. As seen in the left portion of the tracing, the intestine was inactive. About the midportion of the tracing, 26 minutes after the administration of insulin there occurred periodic increases in intestinal activity, consisting primarily in increases in amplitude of intestinal movement.

the intestine, as evidenced by average rises in tone and amplitude of 2.5 and 3.5 mm., respectively. The average duration of the increased activity was 8 minutes.

Ninety-Six Hour Obstruction.—Two observations were made. In each instance, an injection of insulin had been made before the infusion of dextrose preceding the second injection of insulin. In both instances, 40 units of insulin was used. The observations were made 47 and 52 minutes, respectively, after the intravenous injection of the insulin. In each instance, there was a decrease in blood sugar from a normal average value of 209 mg. to 87 mg. per hundred cubic centimeters of blood (58 per cent decrease). In one instance, there was no change in the intestinal activity; in the other, however, there were increases in tone and amplitude of 3 and 2 mm., respectively, which persisted over 8 minutes. The preliminary blood sugar values in the animal in which stimulation of the intestine occurred was 214 mg. as compared with 205 mg. per hundred cubic centimeters in the animal in which no response occurred.

EFFECT OF DEXTROSE PRECEDED BY INSULIN ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Nine observations were made. In seven of these, the blood sugar determinations were complete, so that a correlation between the intestinal activity and the blood sugar could be made. In four not only a previous injection of insulin, but also a previous infusion with dextrose had been made. The interval between the injection of insulin and the appearance of effect on the intestine varied

TABLE 5.—*Effect of Dextrose Preceded by Insulin on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood Sugar	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 9.....	71% T 46.3; A 14.4; T′ 8.3 B 130; B′ 270; +107%	14.8% B 69; B′ 142; +105%	14.8% T 5; A 4; T′ 4.5 B 125; B′ 288; +130%	100% B 119; B′ 263; +142%	.....
24 hr. obstruction; 5....	80% T 50.8; A 7.5; T′ 3 B 128; B′ 263; +105%	20% B 83; B′ 174; +109%	.....	100% B 107; B′ 242; +126%	.....
48 hr. obstruction; 8....	62% T 18; A 11.6; T′ 10 B 71; B′ 249; +264%	25% B 65; B′ 255; +289%	12% T —4; A 1.5; B 121; B′ 200; +64%	100% B 74; B′ 220; +196%	.....
72 hr. obstruction; 12...	83% T 22.2; A 7.8; T′ 8.2++ B 88; B′ 207; +135%	8.3% B 40; B′ 182; +355%	8.3% T 1; A 2; T′ 24 B 48; B′ 102; +112%	83.3% B 75; B′ 218; +178%	16.6% B 104; B′ 96; —17%
				B 80; B′ 179; +124%	
96 hr. obstruction; 5....	60% T 7; A 2; T′ 4.5 B 53; B′ 152; +177%	40% B 105; B′ 209; +99%	.....	100% B 74; B′ 174; +139%	.....

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is given in minutes. The average blood sugar values before (B) and after (B′) the administration of insulin preceded by dextrose are given in milligrams, with the percentage of gain or loss.

between 31 and 125 minutes; in the majority it was between 40 and 80 minutes. Within a very short time after the infusion with dextrose (from immediate response up to 7 minutes), the intestinal effect occurred (fig. 9). In only one instance was the time as long as 25 minutes. In all but two cases, 75 cc. of 10 per cent dextrose solution was used, and in all but one instance, 40 units of insulin was employed. In each instance there was an increase in the blood sugar from a normal average value of 119 mg. to 263 mg. per hundred cubic centimeters of blood (142 per cent increase). The average percentage increases in blood sugar varied from 43 to 288.

In seven (71 per cent) of the nine observations, there was a definite increase in intestinal activity as evidenced by average increases in tone and amplitude of 46.3 and 14.4 mm., respectively. The increases in tone varied from 5 to 85 mm., and the increases in amplitude varied from 3 to 25 mm. The average duration of the increased intestinal activity was 8 minutes. In one instance there was no change, and in another instance there was a decrease in the intestinal activity, there being decreases in tone and amplitude in the latter of 5 and 4 mm., respectively.

Twenty-Four Hour Obstruction.—Five observations were made. In each instance, the time that elapsed between the administration of insulin and the time that observations were made was relatively long, varying from 50 to 83 minutes. In three of the five instances, the original insulin (40 units) was combined with 75 cc. of 10 per cent dextrose solution. In each instance, there was an increase in blood sugar from a normal average value of 107 mg. to 242 mg. per hundred cubic centimeters of blood (126 per cent increase). The percentage increases in blood sugar varied from 108 to 226. There was an increase in intestinal activity in four,

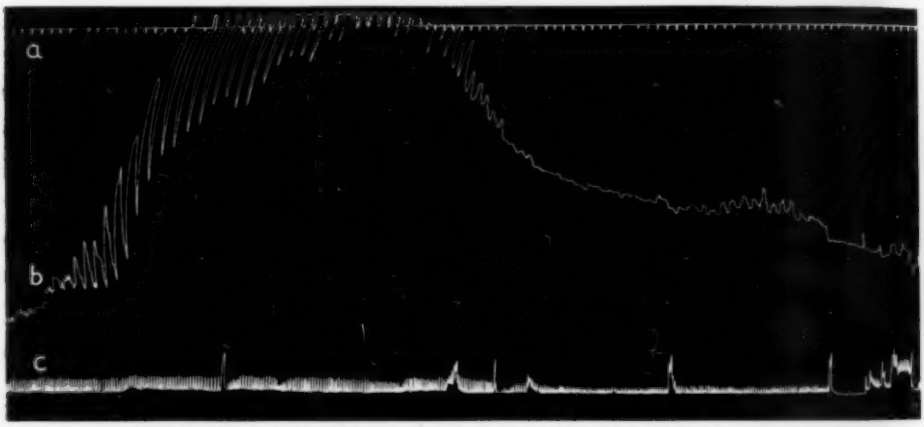

Fig. 9.—Kymographic tracing showing the effect of insulin on a normal intestine. Time, tone and movement of the ileum, and respiration are represented by *a*, *b* and *c*. As shown in the extreme left portion of the tracing, immediately following the completion of the infusion of 75 cc. of 10 per cent dextrose solution there was a marked increase in intestinal activity consisting of an increase in both tone and amplitude of movement.

and no effect was noted in one. The increases in intestinal tone varied from 20 to 88 mm., with an average of 50 mm. The increases in amplitude varied from 2 to 20 mm. and averaged 7.5 mm. The average duration of the increased activity was 3 minutes. In the four instances in which an increase in intestinal activity occurred, the average blood sugar value before the administration of the dextrose solution was 128 mg. per hundred cubic centimeters, whereas the preliminary blood sugar in the one instance in which there was no change in intestinal activity was 83 mg. per hundred cubic centimeters of blood.

Forty-Eight Hour Obstruction.—Eight observations were made. The time that elapsed following the administration of the original insulin varied from 55 to 115 minutes. The time elapsing after the administration of the dextrose solution varied from 2 to 75 minutes. In the majority of instances, however, it was less than 25

minutes. In several instances, a number of infusions, as many as three, of 10 per cent dextrose had been given before the present observations were made. In four instances, 50 cc., and in four instances, 75 cc. of 10 per cent dextrose solution was given after the insulin. The blood sugar was increased in each instance from a normal average of 74 mg. to 220 mg. per hundred cubic centimeters of blood (196 per cent increase). There was an increase in intestinal activity in five observations, and no change in two and a decrease in one. In those instances in which the intestinal activity was increased, the increases in intestinal tone varied from 10 to 28 mm., with an average of 11.6 mm. This increased activity persisted for an average of 10 minutes. In the one instance in which a decrease in activity occurred, there was a decrease in tone of 4 mm., and a decrease in amplitude of 1.5 mm.

Seventy-Two Hour Obstruction.—Twelve observations were made. In all of these, except one, blood sugar determinations were made. In many of the instances, repeated administrations of dextrose were made before the injection of insulin; in seven, two administrations of dextrose were made before the one that followed the injection of insulin. The length of time between the original administration of

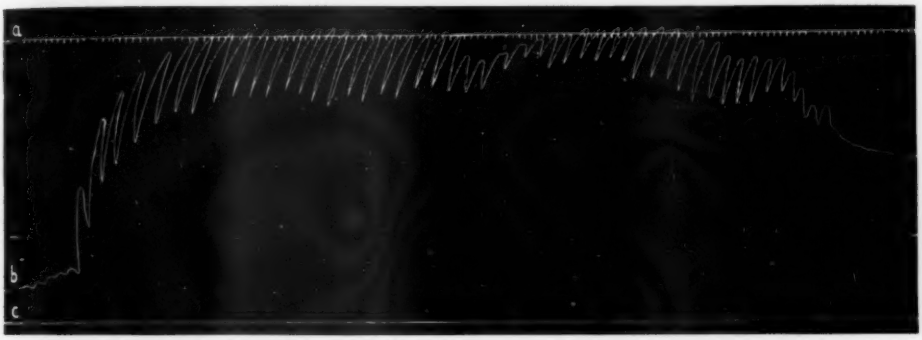

Fig. 10.—Kymographic tracing showing the effect of an intravenous administration of dextrose which had been preceded by an administration of insulin on an intestine that had been obstructed for 72 hours. Time, tone and movement of the ileum, and respiration are represented by *a*, *b* and *c*. As shown in the extreme left portion of the tracing there was no intestinal movement. After the administration of approximately 15 cc. of 10 per cent dextrose solution there was a marked increase in intestinal tone, with an increase in amplitude of intestinal movement. This persisted, following which there was a cessation of movement. The tone, however, remained elevated.

insulin and the present observations varied from 41 to 362 minutes. The length of time from the infusion of dextrose to the observations herein reported varied from 1 to 58 minutes; in the majority of instances, however, the time was between 20 and 30 minutes. With one exception (in which only 10 units of insulin was used), the original amount of insulin employed was 40 units. With but three exceptions (in which 50 cc. was used), 75 cc. of 10 per cent dextrose was employed. In ten (83.3 per cent) of the twelve observations, the blood sugar was increased from an average normal of 75 mg. to 218 mg. per hundred cubic centimeters of blood (178 per cent increase). In two instances (16.6 per cent), a decrease in blood sugar occurred from a normal average of 104 mg. to 86 mg. (17 per cent

decrease). In ten (83.3 per cent) of the twelve instances, there resulted an increase in intestinal activity; the increases in tone varying from 3 to 60 mm., with an average of 22.2 mm.; the increases in amplitude varying from 2 to 25 mm., the average being 7.8 mm. (fig. 10). The average duration of this increased activity was over 8.2 minutes. In one instance there resulted no change in intestinal activity, and in one there were decreases in tone and amplitude of 1 and 2 mm., respectively, which persisted for 24 minutes. The average preliminary blood sugar values were as follows: in those animals in which increased intestinal activity followed the administration of dextrose, 88 mg.; in the one in which there occurred no change in activity of the intestine, 40 mg.; and in the one in which a decrease in intestinal activity occurred, 48 mg. per hundred cubic centimeters of blood.

Ninety-Six Hour Obstruction.—Five observations were made. The length of time by which the administration of insulin preceded the observations varied between 36 and 93 minutes; in the majority of instances it was between 35 and 45 minutes. The time that elapsed between the administration of dextrose and changes in intestinal activity varied from 1 to 50 minutes. In two instances, previous injections of dextrose had been made. In each instance, 40 units of insulin was employed. In two instances, 50 cc., and in three instances, 75 cc., of 10 per cent dextrose solution followed the injection of insulin. There was an increase of blood sugar in each instance from a normal average of 74 mg. to 174 mg. per hundred cubic centimeters of blood (139 per cent increase). In three (60 per cent) of the instances there was an increase in intestinal activity with average increases in tone and amplitude of 7 and 2 mm., respectively. The average duration of this increased activity was 4.5 minutes. In two (40 per cent) instances, no change in intestinal activity followed the infusion with dextrose.

RÉSUMÉ OF OBSERVATIONS

In comparing the effects produced by insulin and dextrose on the motility of the normal intestine and that which had been obstructed for varying periods of time, it was found that the difference in the reactions of the normal and the obstructed intestine to these substances was less marked than would possibly be supposed.

The effects of dextrose alone on the normal and the obstructed intestine were compared. In each instance observed there was a decrease in intestinal activity. There was apparently a less marked decrease in the activity of the intestine obstructed for longer than 24 hours than in that of the normal and that of the 24 hour-obstructed intestine. The average decreases in intestinal tone in the normal and in the 24 hour-obstructed intestine were 27.2 and 38 mm., respectively, as compared with 15 and 10 mm. in the 48 hour and 72 hour obstructions, respectively. Similar but less marked changes occurred in the amplitude of intestinal movement. This would indicate that the depressing effect of dextrose on intestinal activity is more marked in the normal and in the 24 hour-obstructed intestine than in the one that has been obstructed for longer periods of time.

A comparison of the effects of insulin alone on the normal and the obstructed intestine seems to indicate that increased activity occurs

more frequently in the normal intestine and that obstructed for 24 hours than in the one that has been obstructed for longer periods of time. An increase in activity occurred in 100 per cent (1 case each) in both the normal intestine and that obstructed for 24 hours, whereas an increase occurred in 40 per cent, 43 per cent and 66 per cent of those with 48, 72 and 96 hour obstructions, respectively. The number of observations made with the normal intestine and with that obstructed for 24 hours is, however, too small from which to draw definite conclusions. These observations would seem, however, to indicate that the normal intestine and that obstructed for 24 hours are more sensitive to the action of insulin than is the one in which an obstruction has existed for longer periods of time.

The reaction of the normal intestine to the administration of dextrose and insulin combined apparently did not differ from that occurring in one that had been obstructed for varying periods of time.

There was apparently some difference in the reactions of the normal and the obstructed intestine to insulin preceded by dextrose, not as regards the change in activity, but as regards the character of this activity. In those cases in which increased activity (increase in tone) occurred, it was greater in the normal intestine and in that obstructed for 24 hours than in the one that had been obstructed for longer periods of time. The average increases in tone in the normal and the 24 hour-obstructed intestine were 39 and 20 mm., respectively, whereas in 48, 72 and 96 hour obstructions, the average increases in tone were 13.5, 2.5 and 3 mm., respectively.

In comparing the effects that dextrose preceded by insulin had on the normal and the obstructed intestine, it is apparent that increased intestinal activity, as evidenced by increase in tone and amplitude, is more marked in the normal and the 24 hour-obstructed intestine than in the one obstructed for longer periods of time. The average increases in tone in the normal and the 24 hour-obstructed intestine were 46 and 50 mm., respectively, whereas the average increases in 48, 72 and 96 hour obstructions were 18, 22 and 7 mm., respectively. Suggestive similar differences exist as regards increases in amplitude, which, however, are less marked.

Of all the observations made concerning the effects of insulin on the activity of the normal and the obstructed intestine, 55.5 per cent concerned an increase in intestinal activity; 38.8 per cent, no change, and 5.5 per cent, a decrease in activity. In those instances in which an increase in activity occurred, there were average increases in tone and amplitude of 7.2 and 3.8 mm., respectively. The average duration of time of this increased activity was 6.1 minutes. In the one instance in which a decrease in activity occurred, there was a decrease in tone of 10 mm., which persisted for 47 minutes. In each instance there was

a decrease in blood sugar from an average normal value of 118 mg. to 75 mg. per hundred cubic centimeters (36 per cent decrease). It may be significant that the original average blood sugar value in those instances in which increased activity occurred was 129 mg. per hundred cubic centimeters of blood as compared with 96 mg. and 112 mg., respectively, in those in which there occurred no change and those showing a decrease in activity.

TABLE 6.—*Summary Showing the Effect of Insulin and Dextrose Separately or in Various Combinations on the Activity of the Intestine*

Nature of Injection; Number of Observations	Intestine			Blood	
	Increase	No Change	Decrease	Increase	Decrease
Insulin alone; 17.....	55.5% T 7.2; A 3.8; T′ 6.1 B 129; B′ 84; −27%	38.8% B 96; B′ 47; −51%	5.5% T 10; A 0; T′ 47 B 112; B′ 62; −44.6%	0	100% B 118; B′ 75; −36%
Dextrose alone; 16.....	.....	.....	100% T 22.9; A 6.9; T′ 8++ B 135; B′ 260; +92%	93% (13) B 126; B′ 269; +113% B 135; B′ 260; +92%	7% (1) B 250; B′ 149; −40%
Dextrose and insulin; 10	44.5% T 2; A 2; T′ 2 B 121; B′ 76; −37%	55.4% B 92; B′ 75; −18%	.....	25% (2) B 81; B′ 102; +26% B 103; B′ 79; −23%	75% (6) B 110; B′ 80; −27%
Insulin preceded by dextrose; 10	70% T 12.3; A 3.3; T′ 9 B 187; B′ 95; −49%	30% B 162; B′ 63; −61%	.....	.....	100% (9) B 178; B′ 89; −50%
Dextrose preceded by insulin; 39	70% T 27; A 8.5; T′ 8+ B 92; B′ 221; +140%	19% B 76; B′ 205; +164%	10.8% T 3.5; A 2.5; T′ 10 B 98; B′ 184; +88%	94.8% (34) B 89; B′ 229; +156% B 89; B′ 216; −129%	5.5% (2) B 104; B′ 86; −13%

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is given in minutes. The average blood sugar values before (B) and after (B′) the administration of insulin and dextrose in milligrams, with the precentage of gain or loss.

Of sixteen observations concerning the effects of the intravenous administration of dextrose solution on the activity of the normal and the obstructed intestine, 100 per cent concerned a decrease in activity, the average decreases in tone and amplitude being 22.9 and 6.9 mm., respectively. The average duration of the decrease in activity was more than 8 minutes. In thirteen of the fourteen instances (93 per cent), there was an increase in blood sugar from an average normal value of

126 mg. to 269 mg. per hundred cubic centimeters (113 per cent increase). In only one instance was there a decrease in blood sugar. The blood sugar for the entire group was increased from an average normal value of 135 mg. to 260 mg. per hundred cubic centimeters of blood (92 per cent increase).

Ten observations were made on the effects of dextrose and insulin combined on the normal and the obstructed intestine. In 44.5 per cent the activity of the intestine was increased, whereas in 55.4 per cent there was no change. In those instances in which an increase in activity occurred, there were average increases in tone and amplitude of 2 and 2 mm., respectively. The duration of the increased activity was 2 minutes. In six (75 per cent) of the observations, there were decreases in blood sugar from an average normal of 110 mg. to 80 mg. per hundred cubic centimeters (27 per cent decrease). In only two (25 per cent) was there an increase in blood sugar. It is possibly significant that the average blood sugar value in the group in which increased intestinal activity followed the administration of dextrose and insulin was 121 mg. as compared with 92 mg. in the group in which there occurred no change in intestinal activity.

Ten observations were made concerning the effects of insulin preceded by dextrose on the normal and the obstructed intestine. In 70 per cent there was an increase in intestinal activity, whereas in 30 per cent there was no change. In those instances in which there was increased activity, the intestinal tone and amplitude of movement were increased 12.3 and 3.3 mm., respectively. The average duration of this increased activity was 9 minutes. In every instance there was a decrease in blood sugar from an average normal value of 178 mg. to 89 mg. per hundred cubic centimeters (50 per cent decrease). The average blood sugar value in the group in which increased activity occurred was 187 mg. as compared with 162 mg. in the group in which no change in activity occurred.

Thirty-nine observations were made concerning the effects of dextrose preceded by insulin on the normal and the obstructed intestine. In 70 per cent, there was an increase in activity, consisting of average increases in tone and amplitude of 27 and 8.5 mm., respectively. The average duration of the increase in activity was 8 minutes. In 19 per cent there was no change in activity, and in 10.8 per cent there was a decrease in activity, consisting of decreases in tone and amplitude of 3.5 and 2.5 mm., respectively. The average duration of the decreased activity was 10 minutes. In 94.8 per cent of the instances, there was an increase in blood sugar from an average normal value of 89 mg. to 229 mg. per hundred cubic centimeters (156 per cent increase). In only 5.5 per cent was there a decrease in blood sugar. There was less difference noted between the preliminary blood sugar in those animals

in which an increase, no change or a decrease of intestinal activity occurred than was seen in other experiments. The average values of the preliminary blood sugar were as follows: dogs with increased activity of the intestine, 92 mg.; those in which no change occurred, 76 mg., and those in which a decrease in activity of the intestine resulted, 98 mg. per hundred cubic centimeters of blood.

COMMENT

In view of the results obtained in the present investigation concerning the effects of dextrose and insulin on the motility of the normal and the obstructed intestine, and the results of previous investigators concerning the effects on the motility of the stomach and the colon, it is suggested that dextrose alone, either as a preoperative or as a postoperative measure, should be employed cautiously, as without any exception in the present investigation the intravenous administration of dextrose solution produced a decrease in intestinal activity. The importance of the inhibiting effect of dextrose is probably more apparent than real, for, in the present investigation, even though the decreased intestinal activity averaged longer than 8 minutes, it is probable that in the majority of instances the hyperglycemia produced by the intravenous administration of dextrose solution will be controlled by sufficient autogenous insulin (produced by the pancreas) to compensate for the increased quantity of sugar (Sweeney,[14] Escudero,[15] Quigley, Hallaran and Barnes.[16] That the intravenous administration of dextrose exerts an inhibiting effect on the motility of the intestine is an important clinical fact. Even though in a normal person such inhibition may be of little practical importance, in one with an impending ileus or one in whom intestinal motility is not active, the intravenous administration of dextrose solution may cause paresis of the bowel. The results of the present investigation suggest that the administration of insulin with dextrose solution not only will prevent the inhibiting action of the dextrose but will actually increase the activity of the intestine. This effect is apparently most marked if the dextrose infusion is preceded by a preliminary administration of insulin. The administration of insulin alone, either preoperatively or postoperatively in a nondiabetic patient, however, is probably not justified clinically, because of the danger of producing hypoglycemic shock. If this method is employed, it should be used extremely cautiously, and then one should be guided by blood

14. Sweeney, J. S.: Dietary Factors That Influence the Dextrose Tolerance Test, Arch. Int. Med. **40**:818 (Dec.) 1927.

15. Escudero, P.: Latent Diabetes, Endocrinology **11**:27, 1927.

16. Quigley, J. P.; Hallaran, W. R., and Barnes, B. O.: Variations in Blood Sugar Values of Normal and Vagotomized Dogs Following Glucose Administration, J. Nutrition **5**:77 (Jan.) 1932.

sugar determinations. The inhibiting action of dextrose solutions is not due to the hypertonicity of the solutions, because it has been demonstrated repeatedly, both experimentally and clinically, that intravenous administration of hypertonic salt solution stimulates rather than inhibits the intestine. That hyperglycemia itself is not responsible for the inhibiting effect that dextrose solution has on intestinal activity is evidenced by the difference in the results obtained in those cases in which the administration of dextrose solution was preceded by that of insulin. In the latter cases there was an increase in activity in 70 per cent, with average increases in tone and amplitude of 27 and 8.5 mm., respectively, whereas in the former cases there was a decrease of activity in every instance, with average decreases in tone and amplitude of 22.9 and 6.9 mm., respectively. The lack of correlation between the blood sugar values and the activity of the intestine substantiated the contention that the inhibiting effect of dextrose solution is not due to simple hyperglycemia. Of interest, however, is the fact that rather consistently in the present investigation a more marked increase in intestinal activity occurred following the administration of insulin either alone or in combination with dextrose when the original blood sugar values were high. With but few exceptions, the administration of insulin produced an increase in activity of the intestine in those animals with relatively high blood sugar values, whereas either no change or a decrease in activity occurred in those animals with originally relatively low blood sugar values. The exact mechanism of the inhibiting effect of dextrose alone and the stimulating effect of insulin alone or combined with dextrose is not known. Some investigations [17] indicate that the changes are produced by impulses passing over the vagi. In the present investigation, no attempt was made to determine the part played by the nerve supply in the intestine. Because of the lack of correlation between the blood sugar values and intestinal activity, we are inclined to believe with Quigley and Templeton [7] that alterations in the cell metabolism may occur as a result of the administration of dextrose and insulin before blood sugar changes occur. It is probably for this reason that the most marked activity was obtained in those instances in which the administration of dextrose was preceded by that of insulin. In such cases not only was there an increase in intestinal activity in the majority of observations but also the character of the reaction was marked.

The fact that more prompt response in intestinal activity occurred in the normal intestine and that which had been obstructed for 24 hours than in the intestine that had been obstructed for longer periods of time (48, 72 and 96 hours) is significant. Less significant changes in activity

17. Quigley, Johnson and Solomon.[5] Templeton and Quigley.[6] Quigley and Templeton.[7] Quigley and Templeton.[8] Wilder and Schlutz.[9]

occurred in the intestine that had been occluded for 48 hours or longer, probably because of alterations in the metabolism of muscle cells in the wall of the intestine or because of changes in the cells produced by dilatation of the intestine and possibly toxemia. As a result of these alterations, the irritability and the response to various stimuli including dextrose and insulin may be lowered.

Whether dextrose and insulin exert similar effects on the human intestine is difficult to say, because the exact changes occurring in the intestine are difficult to determine clinically. Careful observation of a large number of patients receiving dextrose and insulin, particular attention being paid to changes in intestinal activity, will be necessary before definite conclusions can be drawn concerning the clinical significance of the experimental observations. It is our own observation that patients with disease of the gallbladder or of the liver, to whom dextrose has been administered because of damage to the liver have had more abdominal distention and not as smooth a convalescence as those with other abdominal lesions. We have always attributed this to operative manipulation of the upper part of the abdomen, but it is possible that the administration of dextrose may have been at least partially responsible for the distention. In the present investigation, much larger doses of insulin (from 10 to 40 units) were employed than would be justified clinically. One should probably never use more than 1 unit of insulin for every 2 Gm. of dextrose. The doses of dextrose used were much smaller (from 1 to 10 Gm.) than those generally employed clinically. This fact may be of clinical significance, for apparently in those instances in which large doses were used the inhibiting effect of dextrose alone was more marked than when smaller amounts were given.

SUMMARY AND CONCLUSIONS

1. Experimentally dextrose and insulin either alone or in various combinations produced marked changes in the activity of the normal and the obstructed intestine.

2. The changes were more marked in the normal intestine and that which had been obstructed for 24 hours than in the one obstructed for longer periods of time (48, 72 and 96 hours).

3. Insulin alone produced an increase in intestinal activity (both in the normal and in the obstructed intestine) in 55.5 per cent, the average increases in tone and amplitude being 7.2 and 3.8 mm., respectively.

4. Dextrose alone caused an inhibition of intestinal activity (both in the normal and in the obstructed intestine) in every instance (100 per cent), the average decreases in tone and amplitude being 22.9 and 6.9 mm., respectively.

5. Dextrose and insulin combined resulted in an increase in intestinal activity in 44.5 per cent and no change in 55.4 per cent.

6. Insulin preceded by dextrose produced an increase in intestinal activity in 70 per cent and no change in 30 per cent. The average increases in tone and amplitude were 12.3 and 3.3 mm., respectively.

7. Dextrose solution preceded by insulin produced an increase in intestinal activity in 70 per cent, with average increases in tone and amplitude of 27 and 8.5 mm., respectively. In 19 per cent there was no change, and in 10.8 per cent there was a decrease in activity.

8. The experimental results indicate that dextrose solution exerts an inhibiting effect on both the normal and the obstructed intestine which can be largely obviated by the use of insulin. It is suggested that clinically dextrose alone be used cautiously, and that it be combined with insulin in order to minimize the inhibiting effect it may have on the intestine.

EFFECT OF ALKALIS ON EXPERIMENTAL PEPTIC ULCER

JACOB MEYER, M.D.
AND
HENRY H. RUBIN, M.D.
CHICAGO

The use of alkalis in the treatment of peptic ulcer is based on the assumption that the complete neutralization of hydrochloric acid by the administration of alkalis renders gastric peptic digestion inactive, and the granulation tissue of the ulcer heals.

The purpose of the present study was to determine the effect of the administration of alkalis on experimental peptic ulcer as produced by Mann and Williamson.[1] These observers were able to produce ulcers in dogs by surgical duodenal drainage; i. e., the junction of the pylorus and duodenum was severed and the duodenal end closed. The duodenojejunal angle was located, and the jejunum was followed down for a distance of from 10 to 15 cm., at which point it was transected. The proximal end of the jejunum was anastomosed into the terminal portion of the ileum from 20 to 30 cm. from the cecum by means of an end-to-side anastomosis. The distal end was sewed to the pylorus. Ulcer occurred at the site of the junction with the pylorus in from one day to three weeks. These dogs lived from one day to several months.

Healing of the experimental ulcer was brought about by Mann[2] by occlusion of the pyloric opening proximal to the ulcer, which prevented the passage of the gastric contents over it, and the stomach was drained by means of gastrojejunostomy, the stoma in the jejunum being from 25 to 30 cm. from the ulcer. Mann found also that the drainage of the duodenal secretions back into the ulcer-bearing loop of the jejunum caused healing. The rate of healing was slower and the process more irregular as compared to the other procedure in which the ulcer was completely protected from the gastric secretions. The dogs lived from ten to fifteen days after the operation in most instances. However, some lived from twenty to thirty days thereafter.

As far as we can determine, no attempt has been made to bring about healing of this type of ulcer by medical means.

From the University of Illinois, Department of Medicine, the Nelson Morris Institute, and the Stomach Study Group, Michael Reese Hospital.

1. Mann, F. C., and Williamson, C. S.: Ann. Surg. **77**:409, 1923.
2. Mann, F. C.: S. Clin. North America **5**:753 (June) 1925.

Morton [3] was able to study the reparative process of these ulcers roentgenologically following gastro-enterostomy.

Dragstedt and Vaughn [4] found that alkalis in amounts sufficient to neutralize gastric secretions promote the healing of experimental gastric ulcers. They produced these ulcers by injecting 4 per cent silver nitrate into the gastric mucosa and then placing from twenty to thirty sutures of heavy linen thread in this area; the sutures, extending through the muscularis, were tied loosely and the cut ends permitted to extend into the lumen of the stomach. In four of six dogs chronic ulcers developed three and four months after operation. Then various combinations of sodium bicarbonate, calcium carbonate and magnesium oxide were given, with the aforementioned results.

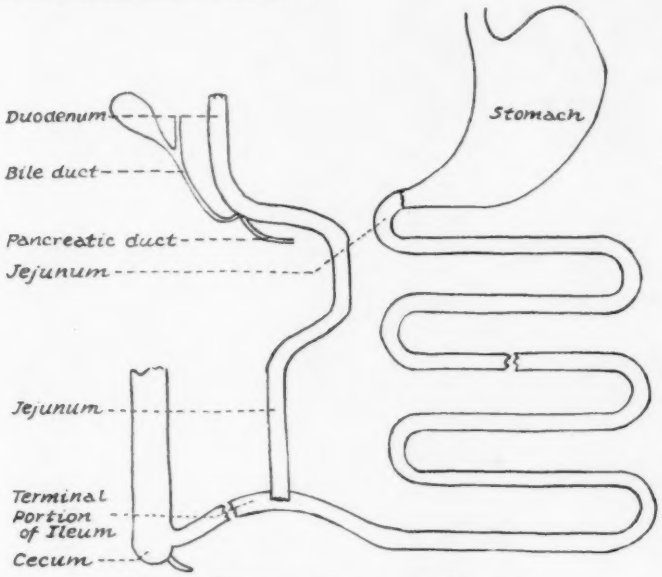

Fig. 1.—Diagram showing operative field.

EXPERIMENTATION

Method.—Peptic ulcers were produced in dogs by surgical duodenal drainage as described by Mann and Williamson (fig. 1). The dogs were reoperated on about three weeks later in order to demonstrate the presence of an ulcer. As soon as they had recovered from the effects of this exploratory operation, feeding of alkalis was begun. Calcium carbonate was chiefly employed. In three instances a combination of sodium bicarbonate, calcium carbonate and magnesium oxide was used. In order to determine whether alkalosis developed, the carbon dioxide

3. Morton, C. B.: Ann. Surg. **85**:207 (Feb.) 1927.
4. Dragstedt, L. R., and Vaughn, A. M.: Arch. Surg. **8**:791 (May) 1924.

Results in Fourteen Dogs

Dog	Date of Operation	Date of Reoperation	Presence of Ulcer	Medication, Amount Used	No. Days Feeding	Date of Death	No. Days Alive after Reoperation	Comment	Postmortem Findings
1	3/15	4/11	+	0	0	4/21	10	Control	Perforating ulcer, peritonitis
2	6/ 1	6/21	+	0	0	6/26	5	Control	Perforating ulcer, peritonitis
3	4/30	5/21	+	0	0	7/31	71	Control	Perforating ulcer, peritonitis
4	6/25	7/16	+	0	0	9/ 4	50	Control	Perforating ulcer, peritonitis
5	7/22	8/12	0	0	0	Killed 1/14 CO gas	147	Control	No ulcer
6	9/ 3	9/24	+	1% HCl, 300 cc. daily	43	11/17	54	.....	Perforating ulcer, peritonitis
7	9/10	10/ 1	+	1% HCl, 300 cc. daily	87	Killed 1/14 CO gas	105	.....	Round ulcer present, adherent to adjacent duodenum with perfect walling off
8	3/10	4/13	+	Calcium carbonate, 180 grains daily	9	4/27	14	Blood chemistry: CO_2, 51 cc. per 100 cc. plasma	Perforating ulcer, peritonitis
9	3/13	4/17	0	Calcium carbonate, 180 grains daily	49	Killed 9/5 CO gas	141	Gastric analysis: 6/13, no acid; 6/14, free 13, total 68; 6/15, free 24, total 33. Blood chemistry: 5/17, CO_2, 30 cc. per 100 cc. plasma	No ulcer
10	4/13	5/ 7	+	Calcium carbonate, 180 grains daily	22	6/ 5	29	Blood chemistry: 5/7, CO_2, 55 cc. per 100 cc. plasma	Perforating ulcer, peritonitis
11	4/26	5/17	+	Calcium carbonate, 180 grains daily	23	6/15	29	Blood chemistry: 5/17, CO_2, 33 cc. per 100 cc. plasma. Gastric analysis: 6/13, no acid; 6/14, free 0, total 23	Perforating ulcer, peritonitis
12	5/14	6/16	+	Magnesium oxide, sodium bicarbonate, calcium carbonate, 90 grains of each	24	7/22	36	.....	Perforating ulcer, peritonitis
13	10/30	11/19	+	Magnesium oxide, sodium bicarbonate, calcium carbonate, 100 grains daily of each	6	12/ 1	12	.....	Perforating ulcer, peritonitis
14	12/24	1/14	+	Magnesium oxide, sodium bicarbonate, calcium carbonate, 100 grains daily of each	22	2/13	30	Blood chemistry: 1/19, CO_2, 35 cc. per 100 cc. plasma; 2/6, CO_2, 50 cc. per 100 cc. plasma	Perforating ulcer, peritonitis

content of the blood was determined in several instances. Determinations of the gastric acidity were also made in certain instances.

The amount of alkali and the period of time over which it was given appear in the table.

Two dogs received 300 cc. of 1 per cent hydrochloric acid.

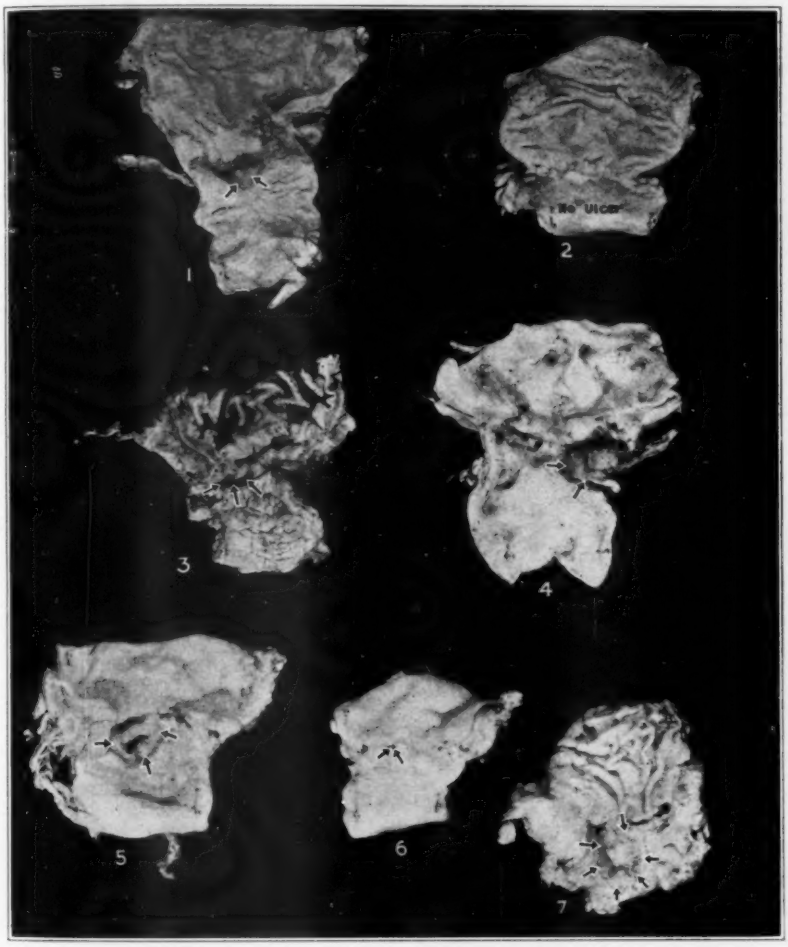

Fig. 2.—Sections showing ulcers and perforation.

Observation and Results.—The total number of dogs operated on was sixty-four. Of these, fourteen survived the first operation. These were used for experimental purposes. In all except two of the fourteen dogs a typical peptic ulcer could be felt and demonstrated at the time of the secondary operation. Dogs 1, 2, 3, 4 and 5, used as controls, received no alkali and lived ten, five, seventy-one, fifty and one hundred and

forty-seven days respectively, after the secondary operation. In dog 5, however, an ulcer did not develop. Seven dogs receiving alkali lived from twelve to thirty-six days following the demonstration of the ulcer. Three of these dogs receiving a combination of approximately 100 grains (6 Gm.) each of sodium bicarbonate, magnesium oxide and calcium carbonate lived thirty-six, twelve and thirty days and were in good physical condition. Of the other four dogs, which received 180 grains (11 Gm.) of calcium carbonate, three lived fourteen, twenty-nine and twenty-nine days, and one that had no ulcer lived for one hundred and forty-one days. The ulcers at autopsy showed no evidence of healing, and death was due to perforative peritonitis. Two dogs were given 300 cc. of 1 per cent hydrochloric acid; one lived fifty-four days, and the other was killed with carbon monoxide gas at the end of one hundred and five days. The first dog died of perforative peritonitis and the second dog showed a healed ulcer walled off by the duodenum.

Chemical examination of the blood did not reveal the presence of alkalosis in any instance. The normal carbon dioxide content of the blood of the dog is between 40 to 50 cc. per hundred cubic centimeters of plasma.

On dog 11 gastric analyses were made a few days before death. No acidity was found on two occasions. In dog 9, in which an ulcer did not develop and which received the same amount of alkali as dog 11, the first analysis showed no acidity, the second analysis on the day following showed 31 degrees of free acidity and 68 of total acidity, and the third analysis a day later revealed 24 degrees of free acidity and 33 of total acidity.

In every animal that died postmortem examination showed a perforated peptic ulcer with generalized peritonitis.

SUMMARY

An attempt was made to study the effect of alkalis on experimentally produced peptic ulcers. The results do not support the view that alkalis are a factor in aiding the healing of ulcer. The dogs receiving alkali did not live longer than the controls that received no alkali. The end-results were the same, perforation and peritonitis occurring in all. The administration of large amounts of 1 per cent hydrochloric acid apparently had no influence in hastening the perforation of the ulcers.

REACTIONS OF THE RAT TO AVERTIN CRYSTALS, AVERTIN FLUID AND AMYLENE HYDRATE

O. W. BARLOW, M.D.
CLEVELAND

Avertin (tribromethanol) was first introduced for clinical use as a crystalline preparation to be administered rectally as a 2.5 to 3 per cent solution in distilled water. The low solubility of the preparation in water (3.5 per cent at 40 C.) necessitates the rectal administration of relatively large volumes of fluid. At temperatures above 40 C. solutions of avertin decompose into hydrobromic acid and dibromacetaldehyde. Owing to these disadvantages, avertin fluid has largely displaced the aqueous solutions for clinical uses.

Avertin fluid contains in each cubic centimeter 1 Gm. of avertin crystals and 0.5 cc. (407.5 mg.) of tertiary amyl alcohol (amylene hydrate). This preparation is said to be more stable than the aqueous solutions of avertin, and the amylene hydrate has been reported to accelerate the rate of absorption of the solute from the rectum. In addition, since the solvent alone is somewhat hypnotic, the combination of avertin and amylene hydrate might result in a summative action; i. e., the solvent, according to Raginsky, Bourne and Bruger,[1] adds to the sedative and anesthetic properties of avertin.

The literature on avertin is extensive, but in practically all of the experimental work and in the majority of the clinical studies a watery solution of the avertin crystals has been used rather than avertin fluid. During the course of another study distinct differences between the effective or sedative dosages of the crystalline or aqueous forms, and the fluid or amylene hydrate solutions of avertin were observed in rats. These observations were at variance with the statements of Raginsky, Bourne and Bruger regarding the results in the dog and in man.

METHODS

Normal adult albino rats were used in all experiments. The "complete sedative action" was determined by recording the tranquilizing effects of the several preparations on the spontaneous movements of the rat when tied down on an animal board. Details of the method have been published elsewhere.[2]

From the Department of Pharmacology of the School of Medicine of Western Reserve University.

1. Raginsky, B. B.; Bourne, W., and Bruger, M.: J. Pharmacol. & Exper. Therap. **43**:219, 1931.

2. Barlow, O. W.: The Tranquilizing Potency of Morphine, Pantopon, Codeine, Papaverine and Narcotine: Results of Tests on the Rat, J. A. M. A., **99**:986 (Sept. 17) 1932.

The premedication dosage was determined by gradually increasing the doses until the animals could be maintained in a reflex-free state for at least thirty minutes in an atmosphere containing 85 per cent of nitrous oxide and 15 per cent of oxygen.

The narcotic or completely anesthetic dosage was considered as that which rendered the animals reflex-free. The most suitable index found was inhibition of the reaction to pain when the hind feet were pinched with a hemostat.

The lethal dosages were determined on a relatively large series of rats because of the marked variability in the reactions of different animals to avertin fluid and to amylene hydrate. The lethal dose was considered as that which kills at least seven of a minimum series of eight animals within six hours with avertin or avertin fluid, or within fourteen hours with amylene hydrate. No differentiation between early and late deaths was deemed necessary.

The preparations were injected either subcutaneously or rectally. The avertin crystals were dissolved in distilled water and administered in a 2.5 to 3 per cent solution. The avertin fluid was administered as 25 to 100 per cent solutions of avertin in amylene hydrate. The amylene hydrate was administered either as an 8 per cent aqueous solution or undiluted.

RESULTS

The table illustrates for the three preparations the observed sedative premedication, narcotic and lethal dosages, as well as the time of induction and duration of sleep and time until complete recovery with sublethal doses and the time until death with lethal dosages. The survivals (O) and deaths (+) with various dosages are illustrated in the chart.

Avertin Crystals, Subcutaneous Administration.—The ratio of the sedative, premedication and narcotic to the lethal dosage was 0.39, 0.58 and 0.62 : 1, respectively. The margin between the sedative and the premedication dose was wide, and intermediate doses produced moderate to deep anesthesia, but complete elimination of the reaction of pain (strong pressure on the foot with a hemostat) required a dose of 450 mg. per kilogram of body weight.

The time of induction was very short, i. e., within from one and one-half to three minutes, and the medium duration of sleep was less than one hour but varied from six-tenths to one and three-tenths hours. Complete recovery required approximately two and one-half hours. Death following the injection of lethal doses usually occurred within one and one-fourth hours, but varied from eight-tenths to two hours.

Rather marked variability between the reactions of different animals to the same dose was noted. Lethal reactions were observed with only 83 per cent of the usual lethal dose, and recoveries occurred exceptionally with doses well above the amount usually lethal.

Avertin Fluid, Subcutaneous Administration.—The reactions to avertin fluid differed markedly from a quantitative standpoint from those noted following the injection of a similar dose of avertin in an aqueous solution. With avertin fluid, the time of induction and duration

Effects of Avertin and Amylene Hydrate on the Rat

Preparation	Mode of Administration	Dose in Mg. per Kilogram of Body Weight				Onset of Sleep with Anesthetic Dose, Minutes		Duration of Action with Anesthetic Dose, Hours				Time of Death with Lethal Doses, Hours	
								Sleep		Complete Recovery			
		Completely Sedative	Premedication N_2O-O_2	Complete Narcosis§	Lethal¶	Average	Range	Range	Average	Range	Average	Range	Average
Avertin crystals 2.5-3% watery solution	Subcutaneous lower abdominal quadrant	275	420	450	730	2.5	1.5-5	0.6-1.3	0.9	1.5-3.5	2.5	0.8-2	1.25
Avertin fluid 1 cc. = 1 Gm. of avertin*	Subcutaneous lower abdominal quadrant	660	960	>960	1,400	35	20-65	1.5-4.0	2.0	4.5->24	5.75	1.2-36	4.75
Amylene hydrate	Subcutaneous lower abdominal quadrant	900	1,050-1,100	1,130	1,400	45	45-120	4.5-12	5.0	10->24	19.0	7-14	9.0
Avertin crystals watery solution	Subcutaneous on one side	275	420	450	730	2.5	1.5-6	1.5-7	2.2	4.5-18	>6	0.4-2.8	1.3
Amylene hydrate†	Subcutaneous opposite side												
Avertin crystals, watery solution‡	Rectal	...	420	550	660-730	3.5	1.5-6	0.4-1.6	1.1	1.5-3	2.2	0.8-1.5	0.9
Avertin fluid	Rectal	325	480	>480	1,375	12	5->20	1.5-2.2	1.45	3.5-24	4.5	0.9-2.2	1.75
Amylene hydrate#	Rectal	...	825	980	1,220	35	20-50	3.5-5	3.5	10->24	12.0	2.5-12	4.0

* 1 cc. of avertin fluid contains 1 Gm. of avertin crystals and 0.5 cc. (407.5 mg.) of amylene hydrate.
† The dose of amylene hydrate, injected separately, was adjusted to that of the avertin crystals, so as to be equivalent to the amount of avertin in avertin fluid.
‡ Data from Tunger. Lethal dose is that which killed approximately 70 per cent of a small series.
# Data from Tunger, extended by Barlow.
§ Narcosis was indicated by absence of reaction of pain to pinching feet.
¶ The lethal dose was taken as that which killed at least seven of a minimum series of eight animals.

of sleep and time until complete recovery were markedly prolonged, and the production of a standard reaction, for instance, sedation or narcosis, required considerably higher doses.

The sedative and premedication doses of avertin fluid were two and four-tenths and two and three-tenths times the doses of avertin crystals,

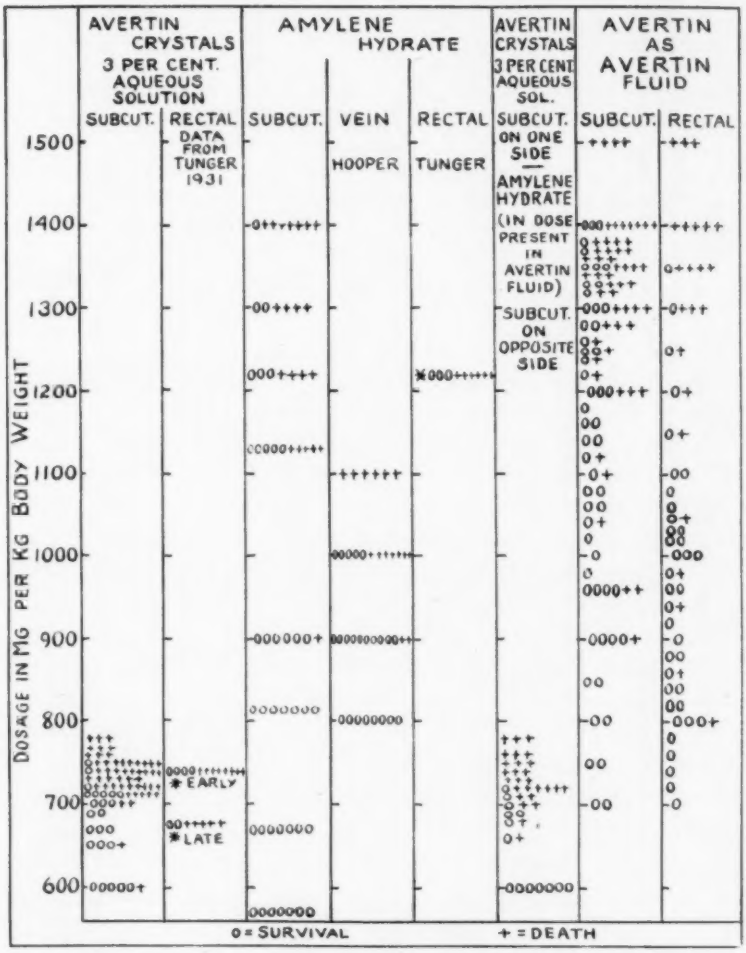

Chart showing survivals and deaths with different dosages.

and the doses required for narcosis or lethal reactions were approximately twice those of the crystals, in spite of the fact that the lethal dose of avertin fluid contains, in addition to 1,400 mg. of avertin crystals, 41 per cent of the minimum lethal dose of amylene hydrate. The variability in the reactions to the amylene hydrate solution of avertin was also markedly greater than in the case of the watery solution.

Amylene Hydrate, Subcutaneous Administration.—Amylene hydrate subcutaneously produces transient irritation, local hemolysis and edema, but no caustic action or slough was observed. The doses required for sedative or complete narcotic effects are quite large, and the margin between the sedative, narcotic and lethal doses is rather narrow.

The time of induction or onset of sleep which is an index of absorption was somewhat longer, while the duration of sleep and the time until complete recovery after narcotic doses or the time to death after lethal doses were from two and one-half to three times as long as was noted with avertin fluid. The lethal dose of amylene hydrate is about the same as that of avertin in the form of avertin fluid, which contains, in addition to avertin, 29 per cent of its weight of amylene hydrate.

The action of the amylene hydrate per se in the dosage ratio present in the completely narcotic dosage of avertin fluid given subcutaneously would result in moderate sedation, a 20 per cent increase in respiratory rate, a somewhat greater decrease in respiratory volume and a 35 per cent depression of minute volume.

Simultaneous Injection of Avertin and Amylene Hydrate.—Although avertin and amylene hydrate act in the same depressive direction, their combination in avertin fluid actually decreases the depression and toxicity for rats to half or less that of the watery solution, as was noted. The nature of this apparent contradiction of reactions was investigated by the subcutaneous injection of various doses of an aqueous solution of the avertin crystals into one abdominal quadrant and at the same time the injection into the opposite quadrant of the quantity of amylene hydrate present in an equal dose of avertin in the form of avertin fluid.

Animals given injections of avertin alone or of avertin and amylene hydrate at separate sites reacted alike so far as induction or depth of anesthesia or toxicity was concerned. The time to complete recovery was distinctly greater in the latter series and indicated that the effects of the longer acting amylene hydrate become apparent after those of the more evanescent avertin are passing off.

These data show that the diminished toxicity of avertin when it is mixed with amylene hydrate is not due to any physiologic antagonism, since it does not occur if the two preparations are injected at different sites. The toxic action must therefore be indirect, presumably by slowed absorption, the amylene hydrate retaining a large part of the avertin at the site of injection, because of the greater solution affinity, until the solvent itself is completely absorbed. The slow recoveries of surviving animals may perhaps involve an additional factor, namely, delayed urinary excretion, since hematuria was observed regularly after medication with moderate doses of either amylene hydrate or avertin fluid. However, this suggestion has not been investigated further.

Avertin Crystals, Rectal Administration.—The rectal administration of a 2.5 to 3 per cent aqueous solution of avertin is not satisfactory in the rat owing to the excessive volume required for studies of toxicity. However, no significant quantitative or qualitative differences in the responses to avertin were noted whether the avertin was administered subcutaneously or rectally. After rectal administration, the time of induction and duration of sleep were slightly longer and the range was wider than after the subcutaneous injection of similar doses. On the other hand, complete recovery from narcotic doses, or death from lethal doses, occurred slightly earlier after rectal than after subcutaneous injection.

Tunger [3] differentiated between the rectal dosages that produce early and late deaths. His fatal dosage for early deaths has been confirmed, but as the difference between the late and the early fatal dosage is only 9.6 per cent, the significance of such a differentiation is questionable. In the present study, fatal reactions occurred within one and one-half hours as a rule; so only early deaths are considered primary.

Avertin Fluid, Rectal Administration.—The sedative, premedication and narcotic doses of avertin in amylene hydrate for rectal administration were between 20 and 25 per cent greater than those required when distilled water was used as the solvent.

These data indicate that small to moderate doses of avertin fluid are distinctly more effective when given by rectum than on subcutaneous injection. The effectiveness of avertin fluid rectally in such doses approaches that of an aqueous solution of the crystals. This greater efficiency of avertin fluid by rectal as compared with subcutaneous administration does not hold for fatal doses, for the fatal doses by the two routes are practically identical in effect. Rectal administration of avertin fluid gives, therefore, a much wider margin of safety between the narcotic and the fatal dose than does subcutaneous administration. This may be explained by the assumption that the absorption of the smaller doses of amylene hydrate is much more rapid from the rectal than from subcutaneous injections, but that, with larger doses, the rectal rate of absorption becomes slowed to that of the subcutaneous injection, and avertin is retained by solution affinity. The matter has not been tested directly, but that amylene hydrate slows the rectal absorption of avertin is indicated by the slower onset of sleep, the wider range of reactions and the longer duration of sleep. Complete recovery from avertin fluid was somewhat earlier (20 per cent) after rectal than after subcutaneous injection, but the duration of action, irrespective of

3. Tunger, H.: Arch. f. exper. Path. u. Pharmakol. **160**:74, 1931.

the mode of administration, was markedly longer than after the development of a similar reaction by means of an aqueous solution of the crystals.

Amylene Hydrate, Rectal Administration.—The rectal dosage of amylene hydrate is slightly (from 13 to 14 per cent) less, the absorption rate is somewhat more rapid and the duration of action is correspondingly shorter than when the preparation is administered subcutaneously. The differences observed were not significant.

CONCLUSIONS

1. The sedative, premedication, anesthetic and lethal doses of avertin crystals, avertin fluid and amylene hydrate have been compared, following both subcutaneous and rectal administration to the rat.

2. The effectiveness and toxicity of an aqueous solution of avertin are markedly greater than those of equal doses of avertin dissolved in amylene hydrate, i. e., avertin fluid. This difference in action is due to a distinct delaying effect of the solvent on the rate of absorption of avertin.

3. The time of induction is slower and the duration of action following the injection of avertin fluid is distinctly greater than after the development of an equal reaction by means of a watery solution of avertin.

4. The slow recovery after the administration of avertin fluid occurs also when the two ingredients are injected at different sites, and is therefore not explainable by delayed absorption; it must be attributed to the persistent depressive effect of the amylene hydrate.

SIMULTANEOUS RESPIRATORY EXCHANGE AND BLOOD SUGAR TIME CURVES

OBTAINED IN APPARENTLY NONDIABETIC PATIENTS WITH NONHEALING WOUNDS

I. M. RABINOWITCH, M.D.
MONTREAL, CANADA

It is a well known fact that surgical wounds tend to heal slowly or not at all in the patient with uncontrolled diabetes. In this phenomenon, one of the surgeons at the Montreal General Hospital, Dr. A. T. Bazin, had the impression that an explanation might be found of nonhealing wounds met with in apparently nondiabetic patients and suggested an investigation of the carbohydrate metabolism in such cases. The experience with the first case so investigated was previously reported.[1] Briefly, the findings, as reported by Dr. Bazin, were as follows:

A female, aged 47, was admitted on Oct. 14, 1924, with an indolent ulcer on the dorsum of the right foot. In August she had suffered a slight abrasion of that area which became infected. The involved area rapidly spread and, in spite of active treatment, the skin sloughed over an area of 5 by 4 inches. After an interval a Thiersch graft was transferred from the thigh, but with no result except that she then had two ulcers instead of one, the thigh wound also failing to heal.

On admission, the ulcers presented an indolent appearance with pale flabby granulations and excessive discharge. The patient was somewhat obese, but otherwise the physical examination was negative in every particular. Repeated urinalysis failed to show any abnormality. The Wassermann test was negative. I taxed my ingenuity to stimulate healing, ringing the changes with various forms of dressings and applications and different modes of physiotherapy. The ulcer would heal almost completely when suddenly the new epithelium would melt away leaving the area of granulation about the same size as when first seen.

Finally, on January 13, two months after admission, an examination of the blood obtained in the fasting state showed a blood sugar of 0.161 per cent—a hyperglycæmia but below the normal urinary threshold. With regulation of the diet this promptly dropped to normal (0.08 per cent); the ulcers healed, and the patient was discharged on February 2, only twenty days after discovery and correction of the real cause of the delayed healing.

In this case, neither the history nor the signs and symptoms suggested diabetes, other than the slow healing of the wound. At no time was there any glycosuria. The patient was readmitted for examination on Dec. 2, 1931, approximately seven years later. There was, again, no

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From the Department of Metabolism, the Montreal General Hospital.

1. Bazin, A. T.: Canad. M. A. J. **23**:146 (Aug.) 1930.

reason to suspect diabetes. On admission, in the fasting state, the urine was free from sugar and acetone bodies, the blood sugar was 0.116 per cent, and the plasma cholesterol was 0.187 per cent. On the following day, a blood sugar time curve was obtained, following the administration of 100 Gm. of dextrose, with the following results:

Time	Blood Sugar
Fasting state	0.114 per cent
30 minutes after dextrose	0.126 per cent
60 minutes after dextrose	0.116 per cent
120 minutes after dextrose	0.111 per cent
180 minutes after dextrose	0.100 per cent

Following this experience, analysis of the blood sugar has been a routine procedure in cases in which a similar condition has been suspected. A common finding is mild hyperglycemia, in spite of the fact that all examinations of the blood sugar are, as a routine, made in the morning in the fasting state, from twelve to fifteen hours after the last meal; the blood sugars usually range between 0.13 and 0.16 per cent. That these findings are not accidental may be seen from repeated analyses of the blood made at different intervals of time. The results in a case met with recently are cited as an example:

Date	Blood Sugar, per Cent	Time Interval Between Tests, Days
February 16	0.143	
17	0.139	1
19	0.131	2
22	0.137	3
29	0.140	7
March 7	0.149	14

Because of these experiences, when blood sugars during fasting were found normal in suspected cases, a more detailed study of the carbohydrate metabolism was made with the use of blood sugar time curves following the administration of dextrose. With this practice, it was found in many cases that, though the fasting blood sugars were normal, the curves indicated disturbed carbohydrate metabolism. Treatment of these patients with diet and insulin led, in the great majority of cases, to healing.

Because of routine precautions, technical error is excluded with respect to the estimation of blood sugar, and the routine method for obtaining blood sugar time curves has also minimized the vagaries of this test. It may be observed that merely giving a person 100 Gm. of dextrose by mouth and making examinations of the blood sugar at periodic intervals may lead to almost any type of curve—normal in the abnormal and abnormal in the normal person. A variety of precautions is essential. In addition to accuracy of the estimation of blood sugars, preparation of a palatable drink and accurately timed collections of blood

are among the many variables which have to be considered in the interpretation of such curves. Some of these were dealt with previously by Rabinowitch and Bazin.[2]

Prompted by these experiences in the surgical wards, the gynecologic service attempted to find an explanation for nonhealing wounds met with in cases of "birth trauma" and as a result of an intensive routine investigation, a fairly high incidence of the aforementioned condition was met with; though wounds failed to heal at the normal rate prior to treatment, with diet and insulin therapy, wounds would heal at the normal rate. That the number of such cases is appreciable is suggested by the fact that eighteen patients were discovered in this service during 1931 alone.

For some time, in spite of the experiences described, I was skeptical about the value of insulin in these cases. Since the discovery of insulin, there has been an increasing literature with respect to the use of this therapeutic agent in conditions other than diabetes. These conditions have included gastro-intestinal disturbances in children, postoperative vomiting, vomiting during pregnancy and others. More recently, insulin has been given as an antiemetic [3] and also has been advised in the treatment of gastric ulcer.[4] In 1928, Rabinowitch and Bazin [5] made a study of blood sugar and respiratory metabolism time curves of normal persons following the simultaneous administration of dextrose and insulin. From the results obtained, it was concluded that, unlike its effects on diabetic persons, insulin did not increase the rate of oxidation of administered carbohydrates in normal persons. As a matter of fact, a decreased rate was observed, and it was suggested that insulin not only does not enhance oxidation of sugar in the normal person, but, in some as yet unexplained way, interferes with the normal mechanism. The data seemed to fit in with those previously obtained by others in animal experiments. Macleod observed that there is a striking difference between normal and diabetic persons, and that the endogenous supply of insulin is always at an optimum in the normal animal.[6] The only reason, therefore, for the use of insulin in the present series of cases was that, though the patients did not appear to be diabetic, there was no doubt about some abnormality of the carbohydrate metabolism, and, though skeptical for some time, with the accumulation of a fairly large number of cases it would appear that the relationship observed between treatment and result was causal and not accidental.

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2. Rabinowitch, I. M., and Bazin, A. T.: Ann. Surg. **94**:354, 1931.
3. Elias, H., and Violin, E.: Ztschr. f. d. ges. exper. Med. **59**:61, 1928.
4. Code, A., and Barral, P.: Monde méd., Paris **40**:497, 1930.
5. Rabinowitch, I. M., and Bazin, E. V.: J. Biol. Chem. **80**:723, 1928.
6. Macleod, J. J. R.: Carbohydrate Metabolism and Insulin, New York, Longmans, Green & Co., 1926.

It is of interest to observe that some of these patients were remarkably resistant to insulin. The usual dosage in such cases is 5 units every six hours, in accordance with our experiences with diabetes that small amounts of insulin given at frequent intervals control blood sugars much better than large amounts given at less frequent intervals. We now have a number of records at the hospital which show that some of these patients, though apparently not diabetic, were able to tolerate as much as 15 units of insulin every six or eight hours, that is, from 45 to 60 units of insulin a day, in spite of the absence of marked hyperglycemia; as previously stated, the blood sugars ranged between 0.13 and 0.16 per cent. We also had a number of cases showing resistance to the same doses of insulin, though the blood sugars obtained in the fasting state were normal. In these cases, the disturbed carbohydrate metabolism was detected by the use of blood sugar time curves.

In view of the foregoing observations, it was considered of interest to make a further study of the carbohydrate metabolism. The method employed was that which has been in use in this laboratory for a number of years. It was first applied in our laboratory to a study of renal glycosuria,[7] and since then has become a standard procedure, hundreds of such tests having now been made. The method consists of a simultaneous determination of blood sugar and respiratory metabolism time curves following the ingestion of dextrose. That it is an ideal method of studying carbohydrate metabolism may be seen from the following observations.

Blood sugar time curves, when obtained without simultaneously determined respiratory metabolism curves, yield limited, though useful, information. The only indications of a hyperglycemic response to dextrose are (*a*) that the dextrose ingested, or at least part of it, has been absorbed, and (*b*) the degree of hyperglycemia is some indication of tolerance, namely, an index of the disproportion between the rate at which dextrose is being absorbed from the alimentary canal and the rate at which it is being utilized. (By utilization is meant the combined mechanisms of oxidation and storage.) The respiratory metabolism is a quantitative index of oxidation.

There are many necessary precautions to be taken in order to be reasonably certain that the respiratory quotients obtained during these tests approximate true metabolic conditions. As is well known, the respiratory quotient at the mouth is not necessarily the respiratory quotient in the body tissues. There are many factors, technical, psychologic, etc., which influence quotients and make difficult their interpretation.

7. Finley, F. G., and Rabinowitch, I. M.: Quart. J. Med. **17**:260, 1924.

The possible sources of error and details of the precautions necessary were previously discussed by me.[8] It is therefore unnecessary to repeat them here.

Respiratory exchange and blood sugar analyses were made before and thirty, sixty, one hundred and twenty and one hundred and fifty minutes after the oral administration of 100 Gm. of dextrose. For the calculation of grams of carbohydrate oxidized per hour, urinary nitrogen estimations were not made, because of the uncertainty that the urinary nitrogen obtained at the time of the test represents the protein metabolism of that period. Fifteen per cent of the total calories per hour were allowed for the protein metabolism.[9] The remaining calories, assumed to be derived from the carbohydrates and fats, were apportioned according to the Zuntz-Schumberg tables as modified by Williams, Riche and Lusk.[10] The results of such a study, including the blood sugar time curves obtained at the time of the test, are recorded in table 1.

TABLE 1.—*Respiratory Metabolism and Blood Sugar Time Curve Obtained Simultaneously Following Ingestion of Dextrose* *

Period	Respiratory Exchange, Liters per Hour		Respiratory Quotient		Calories		Grams of Carbohydrate Oxidized per Hour	Blood Sugar, per Cent
	Oxygen Consumption	Carbon Dioxide Production	Total	Non-protein†	Per Hour	Percentage Increase Above Basal		
Fasting.....	11.65	9.67	0.830	0.835	55.72	..	5.0	0.113
Given 100 Gm. of dextrose in 250 cc. of water flavored with lemon juice								
30 min. later.....	12.09	9.71	0.804	0.802	57.44	3	3.9	0.172
60 min. later.....	12.28	10.06	0.818	0.822	58.59	5	5.2	0.232
120 min. later.....	12.48	9.91	0.794	0.794	58.98	6	3.6	0.250
150 min. later.....	11.87	9.69	0.817	0.818	56.65	2	4.6	0.244

* The patient was a woman, aged 36.
† Calculated by allowing 15 per cent of the total heat production for protein metabolism.

It will be observed that there was a definite decrease in the rate of oxidation of carbohydrates, according to: (*a*) the respiratory exchange, (*b*) the grams of carbohydrates oxidized per hour and (*c*) the specific dynamic action of the ingested dextrose; there was no increase of the respiratory quotient, compared with the normal of 0.12, and the maximum increments of oxygen consumption and carbon dioxide and heat production were 4, 7.1 and 5.8 per cent, respectively, compared with the normal averages of about 12, 25 and 14 per cent. The maximum amount of sugar oxidized per hour was 5.2 Gm., compared with the normal of 10 Gm. or more.

In all, twenty cases were similarly investigated. Because of possible sources of error met with, namely, overventilation, apprehension, restlessness and cough, the results of only thirteen experiments were

8. Rabinowitch, I. M.: J. Clin. Investigation **2**:143, 1925.
9. Voit, E.: Ztschr. f. Biol. **41**:188, 1901.
10. Williams, H. B.; Riche, J. A., and Lusk, G.: J. Biol. Chem. **12**:349, 1912.

regarded as satisfactory and comparable with the normal. A summary of the results is shown in table 2. The data appear to indicate defective carbohydrate metabolism in the group, as a whole, though the findings were normal in some cases. It must be observed, however, that the number of observations was small, and that there was a wide range between maximum and minimum values. This applies also to the standards with which the results were compared. It was therefore considered advisable to test the data still further by a more detailed statistical analysis.

In their "Food Ingestion and Energy Transformations," Benedict and Carpenter [11] recorded all of their results obtained in normal subjects. Because of the completeness of the necessary details, the data lend themselves readily to statistical treatment. Tables 126 to 135, inclusive,

TABLE 2.—*Minimum, Maximum and Average Increments Above Basal Level, Following Ingestion of 100 Gm. of Dextrose*

	Respiratory Quotient*			Carbon Dioxide Production†			Oxygen Consumption†			Heat Production†			Grams of Carbohydrate Oxidized per Hour
Subjects	Low	High	Average	Low	High	Average	Low	High	Average	Low	High	Average	
Normal....	0.07	0.18	0.126	12.3	35.0	24.5	2.9	21.3	11.9	6.1	24.2	14.0	10+
Average of all abnormal cases	0	0.18	0.095	4.0	27.2	16.8	3.5	17.8	8.3	5.8	16.5	9.8	

* Total increase above basal.
† Percentage increase above basal.

afford determination of the maximum increments of the respiratory quotients, oxygen consumption, carbon dioxide production and heat production observed in each experiment. Arithmetical means, standard deviations and probable errors of means were, therefore, readily calculated. Our own data were treated similarly. The combined results are shown in table 3 and are summarized in table 4.

From the ratios of the differences between the means to the probable errors of the differences (table 4), it is concluded that it is highly probable that the differences noted between the normal and our cases in this study were not due to chance alone. Conservative statistical practice, in interpreting differences between means, requires that a difference should be at least four times its probable error before one can assume certainty. The probability, however, that the differences noted between the normal and the abnormal cases were not due to chance alone is increased by the findings with the blood sugar time curves. The results of diet and insulin therapy appear to indicate a causal, rather than an accidental, association between defective carbohydrate metabolism and delayed healing of wounds.

11. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations, Washington, D. C., Carnegie Institution, 1918, publ. 261.

TABLE 3.—*Statistical Analysis of Data on Respiratory Exchange Obtained in Normal and Abnormal Subjects Following Ingestion of 100 Gm. of Dextrose*

Normal

Subject	Respiratory Quotient × 100 Basal (b)	Maximum (m)	Increase (m—b)	Oxygen Consumption, Cc. per Min. Basal (b)	Maximum (m)	Increase m/b × 100	Carbon Dioxide Production, Cc. per Min. Basal (b)	Maximum (m)	Increase m/b × 100	Heat Production, Calories per Min. Basal (b)	Maximum (m)	Increase m/b × 100
K.H.A.	84	101	17	223	240	107.6	187	235	125.6	1.08	1.21	112.4
J.C.C.	74	81	7	252	272	107.9	187	210	112.3	1.19	1.28	107.6
J.C.C.	79	94	15	232	272	117.2	184	242	131.5	1.11	1.33	119.8
L.E.E.	78	96	18	236	255	108.0	183	237	129.5	1.13	1.26	111.5
C.H.H.	87	94	7	193	231	119.7	167	203	121.6	0.94	1.12	119.1
H.L.H.	82	98	16	224	256	114.3	183	230	125.7	1.08	1.24	114.8
P.F.J.	84	99	15	238	245	102.9	200	239	119.5	1.15	1.22	106.1
B.M.K.	70	79	9	217	243	112.0	152	188	123.7	1.02	1.16	113.7
A.J.O.	87	96	9	253	308	121.3	220	297	135.0	1.24	1.54	124.2
Dr.P.R.	78	91	13	186	202	108.6	146	177	121.2	0.89	0.99	111.2
Arithmetical mean			12.6			111.9			124.5			114.0
Standard deviation			4.2			6.02			5.6			5.6
Probable error of mean			0.92			1.30			1.22			1.22

Abnormal

Subject	Respiratory Quotient × 100 Basal (b)	Maximum (m)	Increase (m—b)	Oxygen Production, Liters per Hour Basal (b)	Maximum (m)	Increase m/b × 100	Carbon Dioxide Production, Liters per Hour Basal (b)	Maximum (m)	Increase m/b × 100	Heat Production, Calories per Hour Basal (b)	Maximum (m)	Increase m/b × 100
4699/31	83	83	0	11.65	12.48	107.1	9.67	10.06	104.0	55.72	58.98	105.8
2975/31	86	94	8	9.40	10.34	110.0	8.09	9.74	120.4	45.33	50.95	112.4
4381/31	79	91	12	11.77	12.43	105.6	9.25	11.20	121.1	55.67	60.47	108.6
4006/31	81	91	10	11.20	11.91	106.3	9.12	10.90	119.5	53.33	58.17	109.1
4445/31	79	84	5	11.32	11.91	105.2	9.00	10.02	111.3	53.67	57.19	106.5
5326/31	80	88	8	12.57	14.35	114.1	10.02	12.38	123.5	59.58	68.15	114.4
5373/31	78	83	5	14.63	15.15	103.5	11.45	12.66	110.6	69.23	72.59	104.9
53/32	74	92	18	12.06	13.27	110.0	8.91	11.34	127.2	56.45	63.84	113.1
714/32	76	90	14	12.68	13.48	106.3	9.68	11.61	119.9	59.56	64.05	107.5
960/32	85	94	9	13.80	16.23	117.8	11.72	13.26	113.1	66.42	77.41	116.5
592/32	80	95	15	11.28	11.76	104.2	9.04	10.30	113.9	53.59	56.43	105.3
760/32	77	90	13	9.84	11.16	113.2	7.55	9.58	126.4	46.33	53.36	115.1
906/32	80	87	7	11.44	13.48	108.3	9.91	11.68	117.6	59.00	64.09	108.6
Arithmetical mean			9.5			108.3			116.8			109.8
Standard deviation			4.0			4.1			6.8			4.0
Probable error of mean			0.75			0.77			1.27			0.75

TABLE 4.—*Summary of Statistical Analysis of Data on Respiratory Exchange Obtained in Normal and Abnormal Subjects Following Ingestion of 100 Gm. of Dextrose*

Phenomenon	Subject	Arithmetical Mean (a)	Standard Deviation (b)	Probable Error of Mean (c)	Difference Between Means (d)	Probable Error of Difference (e)	d/e
Respiratory quotient*	Normal	12.6	4.2	0.92	3.1	1.19	2.6
	Abnormal	9.5	4.0	0.75			
Oxygen consumption†	Normal	111.9	6.02	1.30	3.6	1.51	2.4
	Abnormal	108.3	4.1	0.77			
Carbon dioxide production†	Normal	124.5	5.6	1.22	7.7	1.76	4.3
	Abnormal	116.8	6.8	1.27			
Heat production†	Normal	114.0	5.6	1.22	4.2	1.43	2.9
	Abnormal	109.8	4.0	0.75			

* Total increment × 100.
† Percentage increment.

COMMENT ON RESULTS

The usual conditions that might explain impaired healing of tissue appear to have been excluded (syphilis, etc.). All conditions which tend to disturb carbohydrate metabolism and which may lead to blood sugar time curves similar to those observed in these cases were also excluded (nephritis, hyperthyroidism, etc.). How are these data, therefore, to be explained? Infection was present in some of the cases. Infection is known to lead to disturbed carbohydrate metabolism in the nondiabetic as well as in the diabetic patient, and Richardson and Levine,[12] in a study of respiratory metabolism in infection, observed that though there was no direct evidence of a defect in the capacity to oxidize carbohydrates in infection, a defect was inferred from the data. Infection, however, does not explain the picture entirely, since many patients showed no infection, at least not according to the usual indications (local condition, fever, leukocytosis, etc.).

Are these subjects diabetic? The blood sugar time curves, respiratory quotients, rates of oxidation of carbohydrates and specific dynamic responses to the ingestion of dextrose differ in no way from those found in diabetes. In the absence of glycosuria, however, one hesitates to place them in this category. Joslin,[13] when advised of our experiences, also stated that he would hesitate to put these patients in the regular group of diabetic patients, though the fasting blood sugars may have reached 0.14 or 0.5 per cent. Langdon Brown,[14] on the other hand, stated quite recently that he is almost prepared to assert that every one with resting hyperglycemia has diabetes. Because of our search for these cases and routine studies, the number is increasing. For this reason, I further hesitate to classify these patients as diabetic, since this would tend to alter the values of mortalities and morbidities and our data would no more be comparable with other clinics for diabetes, and comparable data are essential for proper statistical studies. As stated, the first patient, after having been observed for approximately seven years, proved not to have diabetes. On the other hand, the following experience was met with recently.

REPORT OF CASE

A woman, aged 52, was admitted to the gynecologic service of the Montreal General Hospital on Dec. 24, 1931, for a hysterectomy. Following this operation, the abdominal wound failed to heal at the usually expected rate. There were no signs or symptoms to suggest diabetes, and at no time was there any glycosuria. The blood sugar time curve, however, revealed a marked disturbance of carbohydrate metabolism. Following the institution of dietetic and insulin treatment, the wound healed, and the patient was discharged from the hospital on Jan. 10, 1932. Shortly after discharge, however, both dietetic and insulin treatment were discontinued and the wound broke down. She was read-

12. Richardson, H. B., and Levine, S. Z.: J. Biol. Chem. **63**:465, 1925.
13. Joslin: Personal communication to the author.
14. Brown, W. L.: Post-Grad. M. J. **8**:49, 1932.

mitted on January 25. There was a history of respiratory infection for some days prior to admission, and shortly after admission the signs and symptoms of pneumonia developed.

The interesting finding in this case is that with the onset of the pneumonia, glycosuria appeared and was accompanied by marked hyperglycemia; the blood sugar was 0.400 per cent, and during the febrile course of the disease the patient required 60 units of insulin a day to keep the blood sugar under control. Is it possible, therefore, that many of these people have diabetes; that glycosuria is not observed because the blood sugars are below the renal threshold for dextrose, and that the disease becomes obvious only when these persons are exposed to some injury or infection which causes further loss of carbohydrate tolerance? Because of this possibility, all of these people are, as a routine measure, being referred to our diabetic clinic to be observed at three month intervals. Experiences during the next five years with these cases should clarify the picture. The purpose of this communication was to draw attention to the association between defective carbohydrate metabolism and delayed healing and to the results which may be obtained with a diet and insulin therapy.

ADDENDUM

Since this paper was submitted for publication, the findings of Williams and Dick on the relationship between dextrose tolerance and infection have been published,[15] and, though the problem was approached from a different point of view, the findings are essentially the same as our own. Acute infectious diseases were studied, and it was observed that these may be accompanied by an increase in the height of the blood sugar concentration during fasting and by alteration in the blood sugar curves following the ingestion of dextrose. This applied both to animals and to man. The loss of carbohydrate tolerance may last for some time—weeks or months—and can be improved by the administration of insulin. The authors suggest that in infectious diseases there are often an injury of the islands of Langerhans and the production of a condition somewhat analogous to diabetes; and recovery of carbohydrate tolerance following insulin is explained by immunity to the infecting organism and by regeneration of the islands of Langerhans.

This work was done with the technical assistance of Miss K. Marjorie Mountford, who was responsible for the collection of all of the gas samples and gas analyses, and of Miss F. Matheson, who was responsible for the proper preparation and administration of dextrose drinks and accurately timed collection of specimens of blood and urine.

15. Williams, J. L., and Dick, G. P.: Decreased Dextrose Tolerance in Acute Infectious Diseases, Arch. Int. Med. **50**:801 (Dec.), 1932.

RESULTS OF SURGICAL TREATMENT OF MALIGNANT GOITER

MARTIN B. TINKER, M.D.
ITHACA, N. Y.

The results of treatment of malignant conditions affecting the thyroid may be far better than certain writers would lead one to believe. Moreover, the situation is not hopeless even when the growth has involved surrounding tissues or extended to lymphatic glands. I reported extensive involvement of surrounding tissues in a woman ten years ago; yet she lived over sixteen years following operation and died from apoplexy at the age of 73.[1] This case and two others in which there was secondary involvement of the lymphatic glands of the neck were reported later, and one of the patients is still living and well eleven years following operation; the other lived nine years and was lost from observation. The outlook is encouraging in many of these cases because adenocarcinoma, the most common malignant condition affecting the thyroid, is slow in development; it metastasizes late and is radiosensitive. These facts have been confirmed by the reports of many other recent observers.

Permanent results are influenced to a considerable extent by the same factors which favor satisfactory results in most malignant conditions: location, extent, duration of the disease and type of malignancy, and the skill, experience and methods of the operating surgeon. Of greatest importance, influencing operative results, I believe to be the use of radium and x-rays in combination with electrosurgery.

LOCATION

Growths located in the isthmus or the anterior surface of the gland, relatively distant from the main lymphatics and blood vessels, do not tend to metastasize as early as those deeply located directly over the great vessel and lymphatic trunks. Such location also makes infiltration of important surrounding structures less likely and complete surgical removal more readily possible.

Duration is frequently difficult to determine. Many patients are incredibly unobservant about the development of growths, even in exposed and readily accessible locations. It is obvious that the longer

1. (*a*) Tinker, M. B.: The Desperate Risk Goiter, J. A. M. A. **79**:1291 (Oct. 14) 1922; (*b*) End-Results of Treatment in Certain Forms of Malignancy of the Neck, Ann. Surg. **76**:335 (Sept.) 1922; (*c*) Tr. Am. S. A. **40**:10, 1922.

the disease has existed the greater the likelihood of metastasis and involvement of surrounding tissues and consequent difficulty in removal. The well recognized slow growth of some of these malignant conditions is a decidedly favorable factor. Kocher [2] reported a case existing ten years without metastasis. The known duration of life was fifteen years in a patient coming under my care twelve years following operation in another clinic; when first seen by me the involvement was evidently too extensive for further surgical procedures; yet after radium treatment this patient lived three years longer in relative comfort.

Small growths, particularly encapsulated growths, which have not broken through and malignant areas discovered only by pathologic examination after operation, located within an enlargement apparently benign, are usually favorable. As noted before, large, extensive growths do not preclude many years of comfortable life and a death from other causes. Extension to the neighboring lymphatic glands of the neck is also not necessarily fatal, although such extension would undoubtedly increase the gravity of the situation. Metastatic extensions to distant parts of the body have proved fatal thus far in my experience, although considering the character of some of these growths this would not seem inevitable.

TYPE OF MALIGNANCY

It has long been known that certain goiters, which both clinically and pathologically are apparently benign, may metastasize and cause the death of the patient. Metastasis is most likely to occur in the flat bones. This was first noted by Cohnheim [3] fifty-six years ago. In a most thorough recent discussion of this subject, Barthels [4] quoted eighty-six writers who have reported one or more such cases. The diagnosis was confirmed by microscopic examination in forty-five cases. A postmortem examination was made in about one third of the cases. Most of the additional cases have shown all the clinical characteristics of a malignant condition, and in some of them there has been a relatively satisfactory pathologic examination. There would seem to be no possible question as to the malignant characteristics of these microscopically benign growths. Two such cases have come under my care; in one the patient died of metastasis to the spine, and in the other of intra-abdominal metastasis.

The adenocarcinomas have been found by all observers the most favorable for treatment. Excellent results have also been obtained in many cases of papillary carcinoma. The infiltrating scirrhous car-

2. Kocher, Theodor: Deutsche Ztschr. f. Chir. **91**:197, 1908.
3. Cohnheim: Virchows Arch. f. path. Anat. **48**:547, 1876.
4. Barthels, C.: Ergebn. d. Chir. u. Orthop. **24**:162, 1931.

cinomas and sarcomas have been found hopeless by practically all observers. Even this view may have to be changed. Gottstein [5] has reported a five year cure in a case diagnosed as round cell sarcoma by Professor Winkler of Breslau.

CHARACTER OF TREATMENT

Surgical measures alone have given freedom from symptoms over long periods of time with apparent cure in a few cases. Irradiation alone has given fewer apparent cures in another group of cases. A combination of operation and irradiation has given favorable results in a considerably larger number of cases than operation or irradiation alone. Electrosurgery has not been used for a long enough time to show what permanent results may be expected, but the fact that the electric current seals blood vessels and lymphatics certainly indicates that metastasis will be prevented in most cases. The destruction of malignant cells by the current should also give a better prospect of satisfactory results. A number of writers have pointed out that biopsy or any manipulation may readily dislodge cells of malignant adenoma and cause their dissemination. The use of electrosurgery and gentleness in manipulation seem to me largely to eliminate this risk. Cuts made from photographs and photomicrographs in previous articles [6] show exactly what may be attained in clotting vessels and surface coagulation. In view of these and many other advantages, it seems surprising that so few surgeons are using electrosurgery. Irradiation alone, whether by x-rays or by radium, has not given permanent cure in any of my cases to this date. It is only fair to state that irradiation alone has been used in only those of my cases in which the growth was so located or so extensive that any form of surgical intervention seemed contraindicated. Operation alone has given a four year cure in only one of my cases. Extensive radical operations with excision of the carotid arteries, jugular vein and the vagus nerve by Theodor Kocher and a number of earlier operators were followed with operative recovery, but do not seem to offer any advantage so far as permanent results are concerned. I have removed a large part of extensive growths infiltrating the great blood vessel sheath and the trachea and larynx in five cases. A sufficient amount of tissue was left surrounding the blood vessels to make reasonably certain that rupture of the vessels would not occur. The microscopic pathologic examinations have been confirmed by well known pathologists. The use of radium following these incomplete

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5. Gottstein: Ber. d. Breslauer chir. Gesellsch., Jan. 20, 1932.

6. Tinker, M. B.: Surg., Gynec. & Obst. **52**:508 (Feb. 7, no. 2 A) 1931; Ann. Surg. **94**:587 (Oct.) 1931.

operations has apparently controlled the further extension of the growth and apparently resulted in a cure in three cases. This experience has still further confirmed my belief that more radical operation is not justified. It is evident that gentle handling of the tissue tends to prevent loosening of cancer cells and metastasis; also that tissues sustaining minimum damage from handling would have a better prospect of healing. As thorough eradication of the growth as is possible seems somewhat to increase the prospect of a satisfactory result though irradiation takes care of extensive involvement in many cases if the great bulk of malignant growth is removed. The advantages of electrosurgery seem so apparent that I believe that it should certainly be used in all operations for malignant conditions, even if the surgeon does not choose to use it in all of his operations on the thyroid.

PROGNOSIS

Pessimistic prognoses vary from those of Hertzler [7] and Jackson,[8] who question whether any patient with a real malignant growth of any extent ever recovers, to those of Crile,[9] Rienhoff,[10] Toland and Kroger [11] and Crotti,[12] who believe that when extension through the capsule has occurred operation is useless. Some of these writers advise irradiation without operation; some advise irradiation if there is a pathologic diagnosis of a malignant condition after operation; some advise operation in early cases, and some offer no suggestions as to treatment.

The more optimistic point of view combines operation and irradiation. The number of recent writers who take a more optimistic view as to the possible results in malignant goiter is considerable. For over seventeen years, due largely to the suggestions and encouragement of Dr. Howard A. Kelly of Baltimore, I have been using irradiation in conjunction with surgical intervention. Emboldened by the fact that two of my patients were living over seven years after operation, I made a brief report on the combined methods in 1922.[1a] In 1928, the number of my cases had increased [1b, c] with four patients living five or more

7. Hertzler, A. E.: Diseases of the Thyroid Gland, St. Louis, C. V. Mosby Company, 1922, p. 131.

8. Jackson, A. S.: Goiter and Other Disease of the Thyroid, New York, Paul B. Hoeber, Inc., 1926, p. 156.

9. Crile, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1928, vol. 2, p. 725.

10. Rienhoff, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1929, vol. 6, chap. 1, p. 225.

11. Toland, C. G., and Krager, W. P.: S. Clin. North America **10**:1201 (Oct.) 1930.

12. Crotti, André: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1918, p. 179.

years after combined treatment, three for six years or over, and one for fourteen years; one patient lived for nine years, dying from unknown causes. Since this report a patient, aged 73, has died of apoplexy over sixteen years after operation. In 1927, Bowing [13] reported results from combined treatment at the Mayo Clinic. The same year Portmann [14] compared surgical measures alone, with 9 per cent five year cures; irradiation alone, with no five year cures, and combined treatment, with 22.6 per cent five year cures, at Crile's clinic. In 1928, Pemberton [15] reported with much thoroughness a large series of cases, stating in conclusion that the results of surgical treatment of carcinoma of the thyroid are more encouraging than is popularly believed. He reported 32 per cent of the patients in whom malignant disease was diagnosed before operation as living three years or longer, and stated that probably in no other malignant disease are x-rays and radium so valuable. Operation in conjunction with irradiation has been employed in the Mayo Clinic since 1918. Barthels [16] reported patients free from symptoms for twenty-four, twelve, eleven and six years. The results of irradiation alone are less certainly good. Barthels also advocates exploratory excision for diagnosis, and if sarcoma or carcinoma is found by biopsy, discontinuance of the operation and irradiation are advised. On the other hand, when one deals with malignant papilloma or adenocarcinoma, further operation is justified. Thirty-three per cent of his patients are living over four years following biopsy. Strauss [17] advocates radical excision, including the lymphatic glands, which he finds affected in about one half of his cases. He considers radical operation and postoperative roentgen treatment the method of choice. Ward and Carr [18] reported 14 per cent of patients living without recurrence in cases from Terry's clinic in San Francisco in which there had been a diagnosis of cancer before operation, formerly considered a discouraging group of cases. Holfelder [19] reported 55.5 per cent of his patients free from symptoms after five years by combined operation and irradiation. Bucky,[20] speaking from the standpoint of the radiologist, has recently advocated the combination of electrosurgery and irradiation in treating

13. Bowing, H. H.: Am. J. Roentgenol. **18**:501 (Dec.) 1927.

14. Portmann, U. V.: Radiation Therapy in Malignant Disease of the Thyroid Gland, J. A. M. A. **89**:1131 (Oct. 1) 1927.

15. Pemberton, J. de J.: Ann. Surg. **87**:369, 1928.

16. Barthels, C.: Beitr. z. klin. Chir. **142**:711, 1928.

17. Strauss, L.: Beitr. z. klin. Chir. **148**:40, 1929.

18. Ward, Robertson, and Carr, J. L.: Tr. Am. A. Study Goiter, 1930.

19. Holfelder, H.: Zentralbl. f. Chir. **58**:940 (April 11) 1931.

20. Bucky: Zentralbl. f. Chir. **59**:1393, 1932.

a number of malignant conditions hitherto considered hopeless. There is a difference of opinion as to biopsy. Clute [21] reported fatal pneumonia following biopsy, and expressed the belief that the rate of growth of the tumor is distinctly accelerated. On page 7 of this same article he expressed his belief that "it is never justifiable to incise a potentially malignant adenomatous nodule for biopsy because of the ease with which these tumors gain access to the blood stream." If radio cutting were used, this danger would almost certainly be avoided, by reason of the fact that the current, particularly the medium or slow cutting current, almost certainly seals blood vessels and lymphatics.

PERSONAL RESULTS OF OPERATION AND IRRADIATION

Among the patients operated on and treated by irradiation, the following number of patients were living and symptom-free for the designated period of years: ten for three years, nine for four years, eight for five years, six for six years, five for seven years, two for eleven years and one for thirteen years. One patient died from an unknown cause after nine years and one died from apoplexy at 73 years of age after sixteen years.

Of those with early extension or recurrences, eight died from two months to two and one-half years following operation. These patients were evidently in serious condition with advanced malignant growths, but were given the benefit of the doubt. Four others in apparently equally bad condition have recovered and remained well for several years. Operation has been refused in only five cases. One of these patients with a large apparently adenomatous goiter had complete consolidation of the left lung which was apparently a solid malignant mass, as shown by roentgen examination. One patient died ten days after leaving the hospital, evidently in too serious condition to be benefited by any treatment whatever. In another case the growth was so extensive and firmly fixed, after thirteen years' duration, that operation was evidently contraindicated. Another man with cerebral symptoms had a low fever for six weeks, the cause of which was undetermined by internists. Finally, one patient refused operation.

There were ten cases reported as suggestive of malignant conditions, or in some instances diagnosed as malignant by one pathologist and as doubtful by others. The microscopic slides will be referred to other competent pathologists as soon as convenient. All of these patients are living and apparently well.

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21. Clute, H. M., and Smith, L. W.: Cancer of the Thyroid Gland, Arch. Surg. **18**:18 (Jan.) 1929.

CONCLUSION

In conclusion, I should like especially to emphasize three points:

1. Exceptionally favorable results with slow growing, late metastasizing, radiation-sensitive growths which make up a large proportion of the total malignant growths of the thyroid. If untreated these go on inevitably to a fatal outcome.

2. The value of combined treatment by irradiation and surgical measures, which in the hands of many surgeons in widely separated locations has given a high percentage of cures or at least relatively comfortable life for many years.

3. The great promise of electrosurgery which, by destruction of cancer cells, leaving nonabsorbing surfaces and sealing the vessels and lymphatics, should reduce the likelihood of local recurrence and prevent metastasis.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

E. STARR JUDD, M.D.
ROCHESTER, MINN.

LINWOOD D. KEYSER, M.D.
ROANOKE, VA.

JEAN VERBRUGGE, M.D.
ANTWERP, BELGIUM

ADOLPH A. KUTZMANN, M.D.
LOS ANGELES

ALEXANDER B. HEPLER, M.D.
SEATTLE
AND
ROBERT GUTIERREZ, M.D.
NEW YORK

(*Concluded from page 538*)

URETER

Surgery.—Marion [28] reviewed his ideas on the technic of total ureteronephrectomy. He does not use the large lumbo-abdominal incision. To perform complete nephro-ureterectomy, a lumbar incision and a low abdominal incision are necessary. He employs the lateral vesical route to reach the pelvic ureter, pushing the peritoneum aside, loosening the bladder from the pelvis and approaching the ureter at the level of the vesical wall. A definite procedure cannot always be determined before operation. In some cases the condition is definite and the plan can be outlined before operation, particularly in cases such as those of ureteropyonephrosis. In other cases the necessity for removing the ureter may not be ascertained until the kidney has been examined. Marion expressed the belief that in these cases the most simple procedure is to approach the ureter by the latero-iliac route, somewhat high up, and free the ureter down to the bladder. He also considered secondary ureterectomy that is necessary on account of the condition of the bladder, as in tuberculous or malignant stump of the ureter.

[COMPILERS' NOTE.—Since the arrival of the urographic era an accurate preoperative diagnosis usually has been made, and the technic of

28. Marion, G.: A propos de la néphro-urétérectomie, Bull. et mém. Soc. nat. de chir. **58**:602 (April 30) 1932.

combined ureteronephrectomy has been greatly simplified. The surgeon can outline the procedure of the operation instead of using the traumatizing, large, lumbo-abdominal incision of the past. Marion, Beer, Papin, Gutierrez and others have emphasized the fact that when the pathologic processes of the kidney have involved the ureter, or vice versa, the proper indication is usually to perform ureteronephrectomy by means of two separate incisions, in an effort to remove in a single piece the diseased ureter and kidney; this obviates the further difficulties arising from a ureteral stump left behind at the time of nephrectomy.]

Scholl [29] stated that stricture with obstruction of the ureter is commonly found associated with renal tuberculosis, and partial or complete ureterectomy occasionally has been advocated. The majority of the reports in which removal of the tuberculous ureter was advised were based on reviews of nephrectomy done in the early decades of urologic surgery. Accurate methods of urologic diagnosis, early recognition of the condition present and skilful, rapid technic, giving special attention to the ureteral stump, have reduced the complications frequently occurring in earlier cases and have lessened the indications for ureterectomy. In a review of 1,023 cases of nephrectomy for tuberculosis, Israel stated that the method of treating the ureter has no marked influence on closure of the wound.

With regard to nontuberculous disease, it is generally agreed that the ureter should be completely removed with the kidney in cases of papillary epithelioma of the renal pelvis; an extension or transplant to the ureter occurs in the majority of cases. Each case of nontuberculous, dilated, infected ureter, associated with stones or pyonephrosis, must be treated individually as the condition demands and as the state of the patient permits. The need later for nephro-ureterectomy or ureterectomy arises in only a small percentage of cases. In a report of 475 cases of hydronephrosis and 471 cases of pyonephrosis in which nephrectomy was performed, complete nephro-ureterectomy was done in only 18 of the cases of hydronephrosis. In none of the remaining cases were operations needed on the remaining ureter after nephrectomy. In only 3 of the 471 cases of pyonephrosis was nephro-ureterectomy found necessary and performed.

In most cases, even when the ureter is extremely dilated, it is not necessary to remove it simultaneously with the kidney. In cases in which the ureter and any retained contents are infected and obstruction to the lower part of the ureter occurs, this obstruction must be relieved. If it is impossible to relieve the obstruction by conservative methods, primary nephro-ureterectomy or secondary ureterectomy should be performed.

29. Scholl, A. J.: The Ureter After Nephrectomy, West. J. Surg. **40**:279 (June) 1932.

Four cases of pathologic changes in the ureter after nephrectomy were reported. Various procedures were done in these cases, such as ureterectomy, cauterization and sterilization of the ureteral contents.

[COMPILERS' NOTE.—Simple nephrectomy is sufficient in the treatment of the majority of patients with renal tuberculosis in whom the lesion is confined to the kidney. On the other hand, there are two types of tuberculous lesions in which both the kidney and ureter are involved; in these cases total ureteronephrectomy is usually indicated in order to avoid the common complications of lumbar fistula or incurable tuberculous cystitis. These two types of lesions are readily visualized in a ureterogram. They are the rosary type of tuberculous ureter, in which the ureter is manifestly infiltrated with tuberculous caseous material, and the megalo-ureter, in which there is enormous dilatation of the ureter or definite tuberculous ureteritis and periureteritis.

The part that the ureter plays following nephrectomy presents a problem of significance in modern urology, particularly on account of the many complications that may arise, and because, as was pointed out before, the lesions of the ureter must be treated individually as the condition demands and as the state of the patient permits. If palliative cystoscopic measures do not relieve the pathologic condition, it is evident that the ureteral stump must be regarded as potentially presenting a surgical condition.]

Walters [30] stated that transplantation of the ureters to the sigmoid-colon has been done at the Mayo Clinic since 1912 in the treatment of exstrophy of the bladder and other vesical and urethral abnormalities in which the bladder failed to hold urine. The method used consists of transperitoneal transplantation of the ureters to the sigmoid-colon in separate stages, with an interval of from twelve to fourteen days between operations. The original method of submucosal transplantation reported by Coffey as applying to experimentally transplanted common bile ducts in animals was used. The transplantations were done without the use of tubes or catheters. Eighty-four patients with exstrophy of the bladder, including those with complete epispadias, have been treated at the clinic in this manner. Within the last seven years Walters has operated in 20 of these cases, in 16 for exstrophy of the bladder, in 2 for complete epispadias and in 2 for congenitally deformed or traumatized urethras with total urinary incontinence. One death occurred among the 20 cases.

30. Walters, Waltman: Transplantation of the Ureters to the Sigmoid-Colon for Exstrophy of the Bladder and Other Ureteral Abnormalities with Urinary Incontinence (Unilateral Versus Simultaneous Bilateral Transplantation), Proc. Staff Meet., Mayo Clin. **7**:470 (Aug. 10) 1932.

Experience at the clinic has shown that it is unnecessary to use either tubes or catheters in transplantation of the ureters to the sigmoid-colon if one normal sized ureter is transplanted at a time. In the treatment of exstrophy of the bladder and other congenital abnormalities of the bladder and urethra, with total incontinence, the risk of such operation is far less for young children than that of simultaneous bilateral ureteral transplantation.

Ureteral Reflux.—Lepoutre [31] reported a case of congenital dilatation of the urinary tract in a girl, 10 years of age. She had had unexplained attacks of fever from infancy and pus in the urine. At cystoscopy 500 cc. of residual urine was found, which was difficult to clear of pus. The meatus of the left ureter was dilated; it had a circular orifice, resembling the entrance of a diverticulum; from time to time a wave of contraction passed over it. On the right side, the meatus, which was oblique and of an oval shape, was too wide, and contracted at regular intervals. Cystoroentgenography with collargol showed a reflux and enormous dilatation of the left ureter and pelvis. The bladder was deformed on the right side, and had the appearance of a diverticulum. Because of the rather delicate condition of the patient, only palliative treatment was given. Occasional lavage with collargol clears the urine and prevents febrile attacks. The prognosis in such a case is not favorable, and the patient probably cannot meet the demands of maternity.

Chronic pyuria in a child, as in an adult, requires complete urologic examination. Significant symptoms are lumbar pain at the time there is urgency, and chronic retention. This type of dilatation may involve an isolated portion of the urinary tract, causing megalo-ureter and megalopelvis. In this case it attacked the calices, pelvis and ureteral meatus at the same time, causing reflux. The malformation may not cause any apparent trouble for a number of years until some complication, generally an infection, makes it evident.

[Compilers' Note.—The subject of congenital malformation of the upper part of the urinary tract has been considered recently by Campbell, who has reported unusual cases of this type from the Bellevue Clinic and the Babies' Hospital of New York. It is well known that the so-called pyelitis of childhood, which does not respond to medical treatment, must be considered as the result of congenital malformation of the upper part of the urinary tract. Every newly born child with abdominal pain or urinary symptoms should have a complete urologic examination, including a cystogram. In this particular type of lesion of vesicorenal reflux, when a "golf hole" type of ureteral orifice is

31. Lepoutre, C.: Dilatation de l'arbre urinaire et reflux vésico-urétéral d'origine congénitale, Bull. Soc. franç. d'urol., May 9, 1932, p. 185.

present, and the lesion is characterized by hydro-ureter and hydronephrosis in which the kidney as a rule is practically functionless, the proper indication is usually ureteronephrectomy.]

Tumor.—Fowler [32] reported a case of solitary papilloma of the lower part of the right ureter occurring in a man, aged 42. He had had intermittent hematuria for twenty-five years. The attack before the patient came under observation had lasted continuously for a month. Cystoscopy revealed a large papillomatous growth on the right side of the bladder, close to the vesical outlet. At operation a large tumor was found attached by a narrow pedicle to the right side of the base of the bladder. Numerous small papillomas were clustered about the urethral orifice. These were all cauterized. Thirty-two months later cystoscopy showed the presence of 4 small papillomas, about 1 cm. in diameter, on the anterior wall of the bladder near the vertex and a similar growth on the left lateral wall. At that time treatment was not acceptable, and several years later examination revealed an extensive growth involving the anterior wall and filling the vertex of the bladder. The whole tumor-bearing area was widely resected in one piece. This included the area of normal vesical wall between the separate growths.

The patient had several attacks of hematuria during the next few years, and finally died suddenly. At necropsy the right ureter was dilated to a diameter of 1.5 cm. within 2.5 cm. of the bladder. At this point there was a papillomatous tumor, the base of which was 1 cm. and the villous mass 2 cm. long, projecting into the lumen of the dilated ureter. In the bladder just below the orifice of the left ureter was found another papillomatous mass with a base of 1.5 cm. Just above the urethral orifice were several minute papillomas.

Several interesting points in this case were emphasized. There was a definite history of intermittent hematuria over a period of twenty-five years prior to the patient's coming under observation. The longest period noted in reported cases has been fourteen years. The low grade of malignancy of the growth in the bladder was shown both clinically and histologically, placing it with the so-called benign papilloma group of tumors. The actual involvement of the bladder existed for more than the eleven years that this patient was under observation, as shown by the presence of a large tumor at the first examination and by the long history of hematuria. During this time the character of the growth did not change; it showed no tendency to undergo malignant degeneration. The original tumor had the clinical characteristics of papilloma. Recurrences took place in various parts of the bladder, not at the site of the original growth. The histologic examination of the tumor found

32. Fowler, H. A.: Solitary Papilloma of the Lower Ureter (Right) Secondary to Recurrent Papillomata of the Bladder, J. Urol. **27**:561 (May) 1932.

at necropsy disclosed the type of cellular structure usually seen in papilloma. This observation appears to confirm the view that the type or character of cell in these papillary tumors does not change. If the original tumor is benign, any recurrence that may develop will have the same characteristic.

Mycosis Ureteritis.—Leinati [33] observed a case in which a ureter was the site of primary mycotic ureteritis following the experimental injection of a culture of Aspergillus fumigatus into the spleen of a rabbit. The fungus had not invaded any other region. The spores apparently did not find suitable ground for their development in the spleen, and in passing through the blood stream must have been either destroyed or eliminated through the renal filter without doing any injury until they entered the left ureter. At necropsy, eight days after the injection which caused death, not only was the aspergillosis present in the left ureter, but also dilatation. This dilatation evidently had existed previous to the mycotic infection, as the thickening of the wall of the ureter, especially the muscular hypertrophy, could not have developed in eight days. There was no mechanical obstruction of the ureter, nor was there any inflammatory stenosis caused by advanced ureteritis. The thickening of the wall and the muscular hyperplasia continued down to the bladder, the wall of which was indurated, with hyperplasia of the muscular tunics. The papilla of the ureter was conserved, and the right half of the bladder, with its ureter, presented no changes. It was therefore assumed that the ureterectasia was a primary congenital dilatation, dependent on obstacles of a functional nature or on lesions of the peripheral reno-ureteral nervous system.

The fact that the induration involved the entire urinary tract on the left side indicated that the cause had not been sufficient to diminish appreciably the functional activity of the excretory passages because of the compensatory hypertrophy that had developed. The kidney did not reveal lesions resulting from urinary stasis or from old inflammation, but only those related to aspergillar pyo-ureteronephrosis.

The ureterectasia was undoubtedly the effective cause of the grafting of the aspergillar infection on the ureter. In view of the experimental demonstration of the resistance of healthy urinary passages to infections, primary localization of infection in the urinary excretory passages can occur only when there is an anatomic or functional lesion. The urinary stasis in this case, although moderate, was sufficient to permit the growth and development of the aspergillar infection. As the inflammation spread to the entire wall of the lower third of the ureter, the attacks of acute retention began, leading at length to incoordination

33. Leinati, Fausto: Sopra un caso di ureteropionefrosi aspergillare sperimentale in progressa ureterectasia, Arch. ital. di urol. **8**:55, 1931.

of movements and to spasms, finally resulting in dilatation of the pelvis, compression of the renal parenchyma and disappearance of the papillae. As the stasis and retention increased, the juxtavesical portion of the ureter gave way, and funnel-form dilatation of the lumen was produced. Thus was formed pyo-ureteronephrosis in which Aspergillus fumigatus could develop so well that histologic examination revealed even stages of fructification.

BLADDER

Tumor.—Gunsett [34] reported the cases of 26 patients with carcinoma of the bladder treated by him during seven years. Roentgen therapy was given in divided doses for about three weeks. Only the first patient was treated by means of a single application, 128 per cent of the erythema dose, but distributed over five days. In some of the cases this procedure was preceded or followed by electrocoagulation. Of the 26 patients, 10 are alive and free from symptoms: 1 patient ten years, 1 nine years, 2 eight years, 2 seven years, 1 six years, 1 four years and 1 three years following treatment. Eight (42 per cent) of 19 patients have remained well five years after observation.

Gunsett expressed the opinion that extensive tumors of the bladder should first be treated with deep roentgen rays; electrocoagulation should be employed as a means of destroying any portions of the growth which remain after the first type of treatment. In certain cases roentgen therapy may be used after electrocoagulation which has given imperfect results.

Lazarus and Rosenthal [35] stated that myxosarcoma of the bladder is rare and primarily a disease of early life. Diagnosis is possible only from a histologic study of the tumor, although the finding of small gelatinous-like bodies in the bladder is suggestive of tumor of this type.

Surgical excision does not give satisfactory results because of the prompt recurrence of the growth. Roentgen therapy has an appreciable effect on the neoplasm, as shown from the pathologic report of the authors' case. Coley's serum was found to be of no benefit. Total cystectomy offers the best possibility of cure in these cases.

Diverticulum.—Walters and Mulholland [36] reported a detailed study of 30 cases of diverticula of the bladder.

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34. Gunsett, A.: La roentgenthérapie du cancer de la vessie par la méthode de la dose fractionnée, Acta radiol. **13**:1, 1932.

35. Lazarus, J. A., and Rosenthal, A. A.: Myxosarcoma of the Bladder: Case Report of a Child Two Years of Age, J. Urol. **27**:695 (June) 1932.

36. Walters, Waltman, and Mulholland, S. W.: The Relation of Diverticula of the Bladder to Obstruction of the Vesical Neck, Surg., Gynec. & Obst. **55**:104 (July) 1932.

Urinary obstruction was a symptom in each case. The average duration of the symptoms was eight and seven-tenths years. Dysuria and burning on urination were usually late symptoms, and were accompanied by pain in the bladder and perineum. There was a high degree of infection of the urine in 26 of the cases. The average quantity of residual urine in the bladder was 360 cc. Residual urine was absent in only 1 case. In 10 cases the bladder was so distended as to extend above the symphysis pubis.

On the assumption that diverticula are caused by congenital weakness of the bladder that is manifested because of the obstruction, a study was made to ascertain the evidence of other abnormalities. Hernia existed in half of the cases; obesity was marked in about a third. Diabetes was present in 3 cases, and unilateral complete duplication of the renal pelvis and ureter was found in 1 case.

Diverticula of the bladder in adults practically always are seen in the presence of obstruction at the vesical neck, which undoubtedly accounts for the preponderance of the lesion in men. This series was composed entirely of men. In more than half of the cases, definite fibro-adenomatous hypertrophy of the prostate gland made prostatectomy advisable. The smaller the prostate gland was at operation, the longer the symptoms seemed to have been present. Cicatricial contraction of the vesical neck may occur, and can be remedied by a plastic procedure at the time of diverticulectomy, by a subsequent punch operation or by incision with the Collings knife.

Excision of the diverticulum is the only operation which gives uniformly satisfactory results. Extravesical excision is usually applied to large diverticula that can be separated from the surrounding structures by careful dissection. It was used in 19 of the 30 cases. If there is evidence of marked perivesical inflammation, if the bladder has been previously drained and much scar tissue is present, making extravesical dissection difficult and hazardous because of the possibility of opening the peritoneal cavity, and if the diverticulum is not too large, the transvesical method is indicated. This type of procedure was used in 5 cases.

The results were satisfactory in more than two thirds of the cases in which the diverticulum was removed. In 2 cases the outcome was fair; there was relief from most of the disturbing symptoms. Five patients continue to have dysuria. Removal of a portion of the sclerosed vesical neck by the punch operation did not always serve immediately to relieve the urinary retention. The best results were obtained in cases in which the obstruction at the neck of the bladder was thoroughly removed, either at the time of diverticulectomy or subsequently by prostatectomy or by a punch operation for an obstructing median bar.

Fistula.—Juliá [37] reported the results of transvesical intervention in 3 cases of vesicovaginal fistula. This type of fistula may be approached vaginally, transvesically or transperitoneally. Although most gynecologists prefer the vaginal method, the results are uncertain. The disadvantage of the transperitoneal route of Legueu is that it exposes the peritoneum to infection from the infected bladder. The transvesical procedure of Marion is the most simple method of approach. It is indicated in all cases of vesicovaginal fistula except those involving the neck of the bladder, when the vaginal approach is preferable.

The bladder should be opened widely, placing the separator of Legueu outside of the bladder. The posterior depressor, situated within the vesical cavity, well exposes the lower part of the bladder, which is usually the site of the fistula. Care should be taken not to include the ureteral orifices in some suture, or to cut them when dissecting the mucosa. For the deep stitches the linen type of suture used in gastro-intestinal surgery is preferable, because of its greater resistance, fineness and flexibility, which permit it to be tolerated with little reaction. In the 2 cases in which the results were successful, a linen suture was used; in the third case, which was a failure, catgut was used for both deep and superficial sutures. For the superficial stitches, particularly those in the mucosa, catgut is desirable because of its prompt resorption. There should be perfect coaptation of the sutured margins to prevent infiltration of urine between the stitches. Drainage, which is necessary after these operations, may be either urethral or suprapubic. Juliá prefers suprapubic drainage because it permits the use of a large catheter which is less likely to become obstructed. The catheter should remain in place for from seventeen to nineteen days, according to the degree of infection following intervention.

[COMPILERS' NOTE.—In any operation of reconstruction for vesicovaginal fistula, as well as for any plastic operation on the urethra, one of the most important procedures is urinary drainage by simple cystostomy, regardless of the method used to treat the lesion. This preliminary drainage is generally an important factor in obtaining the best result following a plastic operation.]

Cystitis.—Ravich and Katzen [38] stated that cystitis emphysematosa is more common among females than among males; in only 5 of the 24 cases reported in the literature were the patients males. The disease usually occurs in adult life. Although the etiology of the lesion

37. Juliá, Serrallach: Tratamiento de las fístulas vésico-vaginales por vía transvesical, Rev. españ. de cir. y urol. **14**:159 (April) 1932.

38. Ravich, Abraham, and Katzen, Perry: Cystitis Emphysematosa: Review of the Literature with Report of an Authentic Case Terminating in Recovery, J. A. M. A. **98**:1256 (April 9) 1932.

is not definite, it is believed that bacteria are a significant factor. Macroscopically, there are gas-containing vesicles in the wall of the bladder; these may occur singly or in groups in any portion of the bladder, or may cover the entire organ more or less uniformly. They appear as transparent, rounded elevations which protrude into the lumen of the bladder. Microscopically, desquamation of the epithelial covering of the bladder overlying the vesicles is often observed. In 17 of the 24 cases there were no symptoms in the urinary tract. When such symptoms were present, they were usually due to the accompanying urologic pathologic condition aside from cystitis emphysematosa.

Ravich and Katzen reported a case in which recovery followed surgical intervention.

Surgery.—Walters [8] reported that 164 operations were performed on the bladder; 5 patients died from extensive carcinoma of the bladder during 1931 at the Mayo Clinic. Diverticulectomy was performed in 14 cases; all the patients recovered. Transurethral fulguration of intravesical tumor of the bladder was done in 114 instances without mortality.

PROSTATE GLAND

Hypertrophy.—Marion [39] stated that, in his opinion, the transvesical method of operation in chronic cases of prostatitis is preferable because of the likelihood of perineal fistulas and the difficulty of suppressing all the inflammatory lesions when the lower route is used. The procedure is indicated in chronic cases of prostatitis in which there is mild suppuration which does not respond to any medical treatment, perineal fistula and periprostatitis, calculi or hypertrophy of the gland. Urethrography should be done to confirm the diagnosis and to show any cavities or tracts which had not been suspected.

The type of intervention to be used depends on each particular case. If it is necessary to remove the lobes of the prostate gland with small abscesses, these may be easily enucleated by means of incisions that cross the entire wall of the bladder. The incision in the bladder is made immediately behind the vesical neck, following two oblique lines backward and outward, the knife being guided to a certain extent by the finger in the rectum which is orienting the lobes. When the abscesses are large and open into the urethra or form fistulas into the perineum, it is sufficient to open them widely, depressing the upper wall formed by the bladder and the tissue of the gland which incloses them. If calculi are present, the pockets which contain them should be opened and the stones removed. If suppuration in the prostate gland coincides

39. Marion, G.: De la voie transvésicale dans les affections de la prostate autres que l'hypertrophie et le cancer, J. d'urol. **33**:217 (March) 1932.

with adenoma, the more or less adherent tumor should be removed, which will open the purulent cavity lying below it. After any of these operations the cavity is packed, and a postoperative course similar to that in any ordinary prostatic case is followed.

In some cases preoperative vaccination was given. In 1 instance in which there was much suppuration and no vaccination before operation, generalized infection and death resulted. Marion expressed the opinion that surgical intervention in these cases does not entail any more risk than prostatectomy for hypertrophy of the gland. There were only 2 deaths among 74 patients so treated.

[COMPILERS' NOTE.—The advocates of the suprapubic route and the perineal route for attacking the various pathologic conditions of the prostate gland and seminal vesicles appear to be at variance. It is evident that Marion has obtained satisfactory results by the transvesical method. In many cases of chronic prostatitis and seminal vesiculitis in which there is practically no communication with the bladder, the perineal route secures better drainage with less suffering and shorter hospitalization, and prevents localized infection of the bladder and its ascent into the upper part of the urinary tract. Prostatotomy or vesiculotomy for chronic prostatitis or seminal vesiculitis was well conceived by Fuller. As Gutierrez [40] has shown in a report of 100 consecutive cases in which seminal vesiculectomy was performed without mortality, if the operation is performed extra-urethrally, extravesically and extraperitoneally, there is no danger of complications such as Marion and other supporters of the suprapubic route have emphasized.]

Segurola [41] reported a case in which adenoma of the prostate gland recurred five years after prostatectomy. Unusual features of the case were the extreme hypertrophy of the group of precervical or anterior cells, localization of the tumor above the neck of the bladder and independent of it, attachment of the tumor to a pedicle and the fact that this occurred after prostatectomy, at which time there was no change in the cells of the anterior group. These cells, which were first described by Aschoff, not uncommonly undergo hypertrophy. Young explained why intravesical tumors of the prostate gland sometimes acquire a pedunculated form, but no cases were reported in the literature in which the reproduction of the hypertrophy was localized exclusively in the

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40. Gutierrez, Robert: Later Results of Surgery of the Seminal Vesicles: Report of One Hundred Consecutive Seminal Vesiculectomies, J. A. M. A. **93**: 1944 (Dec. 21) 1929.

41. Segurola, M.: Tumor pediculado localizado por encima del labio anterior del cuello vesical y constituyendo histologicamente un adenoma prostatico en un operado de prostatectomia, con cinco anos de anterior-idad, An. de cir. **4**:344 (May) 1932.

group of ventral cells and appeared to be completely intravesical, independent of the neck of the bladder and simulating a tumor of it.

The provisional diagnosis was sessile tumor of the bladder. Because partial cystectomy was contemplated, the bladder was widely opened, and the tumor was found to be attached to a short pedicle. The growth was removed and a seed of radium was placed within the site of its implantation. The patient made an uneventful recovery. Histologically, the growth was an adenoma of the prostate gland.

[COMPILERS' NOTE.—Recurrence of hypertrophy of the prostate gland after prostatectomy is always of great interest. There are many ways to explain the failures of total prostatectomy, and the sequelae are well known. Cases of reproduction of glandular tissue in the neck of the bladder in which the same clinical symptoms have appeared as were present previous to operation have been recorded from time to time in the literature. Bransford Lewis has recently discussed this phenomenon. It is a fact that in many cases of perineal prostatectomy, for lack of proper exposure, the entire gland is not removed at the first operation, and sometimes a median or a lateral lobe is pushed back into the bladder. This is not detected during enucleation of the gland, and gives rise to a pedunculated lobe of the prostate gland. This lobe may be attached by a small bit of capsular or mucosal tissue to the roof of the neck of the bladder, resulting in definite hypertrophy with clinical symptoms such as Segurola has described. Thomson-Walker has called attention, in suprapubic prostatectomy, to the formation of tags which have been omitted during enucleation of the gland and which later undergo hypertrophy and produce definite mechanical obstruction to the outflow, and even attacks of complete retention such as occurred previous to the operation.]

Treplin and Vogel [42] reported a series of cases of hypertrophy of the prostate gland, most of which were unsuitable for open operation and in which treatment was by transurethral diathermy. These authors developed an instrument similar to a urethral catheter which has a silver band several centimeters from the tip. An eye in the tip makes it possible to determine the position of the instrument. The instrument is inserted into the bladder and withdrawn until the fluid ceases to flow, indicating that the coagulating section or silver band is in the prostatic part of the urethra. At this time the current is turned on, and for thirty seconds the prostatic part of the urethra is coagulated.

In a series of 15 cases there was no mortality, and good functional results were obtained, all patients being able to empty the bladder completely after treatment. In 4 cases there were extensive pulmonary

42. Treplin, L., and Vogel, R.: Ueber weitere Erfharungen mit der Diathermieoperation bei Prostatahypertrophie, Zentralbl. f. Chir. **59**:1284 (May 21) 1932.

complications and myocardial degeneration, but the results were also satisfactory. In 3 cases of carcinoma of the prostate gland it was necessary to perform suprapubic drainage before treating the gland by this method. One patient received no benefit from the treatment; the other 2 were able to empty the bladder completely, and the suprapubic fistula eventually closed.

Davis [43] reported a summary of the immediate operative and the late functional results in a series of 411 consecutive cases of perineal prostatectomy performed under sacral block anesthesia. Nine deaths have occurred in the series. Inquiry several months after operation disclosed that 82 per cent of these patients voluntarily classified themselves as well, 17 per cent as improved and 2 per cent as unimproved. Massive delayed hemorrhage, appearing as late as the end of the second week after operation, occurred in 2 per cent of the cases.

The chief factors contributing toward maintaining a low mortality rate in prostatectomy are adequate preliminary drainage, employment of the perineal route, detailed attention to hemostasis and sacral block anesthesia. The technic of sacral block anesthesia for prostatectomy may be made sufficiently exact to eliminate entirely the percentage of failure which was formerly considered inevitable. Davis has employed sacral block anesthesia for perineal prostatectomy in 262 consecutive cases without failure of the anesthetic in a single case. All of the 411 patients received this type of anesthesia, which consisted of a caudal injection, and injection into the first, second and third posterior sacral foramina.

Walters [8] found that 22 deaths (10 per cent) occurred in a series of 227 cases in which cystostomy had been performed at the Mayo Clinic in 1931. In 135 cases the operation was performed because of urinary obstruction from hypertrophy of the prostate gland. Necropsy revealed that the causes of death were lesions such as coronary thrombosis, acute bacterial endocarditis, pulmonary embolism, coronary sclerosis with occlusion, marked dilatation of the pelvis of the kidney and ureters with renal insufficiency and embolic infarct of the lung pulmonary edema caused the death of 1 patient, aged 80.

Walters expressed the belief that the transurethral method for relieving obstruction due to so-called median bar prostatitis and contracted neck of the bladder is superior to an open operation. At present it is acceptable as a surgical procedure in cases in which there is a slight degree of adenofibromatous hypertrophy of the median and lateral lobes of the prostate gland. If there is considerable hypertrophy of the gland and the condition of the patient is satisfactory, prostatectomy done by a properly trained surgeon will have as low a mortality as any

43. Davis, Edwin: Analysis of Results in 411 Consecutive Cases of Perineal Prostatectomy, Nebraska M. J. **17**:224 (June) 1932.

transurethral procedure. On the basis of pathologic changes in adenofibromatous hypertrophy of the prostate gland, the obstruction is likely to recur unless the adenoma is completely removed.

Bumpus [44] stated that prostatectomy is performed primarily for correction of urinary obstruction in the urethra, rather than because of any change in the prostate gland. The operation of transurethral resection of the prostate gland endeavors to correct the obstruction by removing only the portion which obstructs and not any other tissue. When this obstruction is slight, and in a channel the diameter of which is less than 1 cm., the amount of tissue capable of causing obstruction may be insignificant, and patients have been seen whose urinary retention was completely relieved by removal of less than 1 Gm. of tissue, if such tissue completely blocked the urethra.

In a series of 96 patients with adenofibromatous hypertrophy of the prostate gland treated by transurethral methods during the last seven years, 52 were dismissed as completely relieved of residual urine, as tested by catheter. In 9 other cases there was less than 30 cc. of residual urine, although in 38 cases there was more than 150 cc. before operation, and in 17 complete retention had occurred. Of the 86 patients who are still living, 68 are satisfied with the results. Among the 18 cases in which operation was not successful, prostatectomy has been performed on 4 patients; all these operations were performed more than five years ago.

The beneficial results of the operation depend on the amount of tissue removed. Experience has shown that from 10 to 20 Gm. of tissue may be safely removed from the neck of the bladder if the associated residual urine is completely relieved as a result. If any urine is left, the presence of a denuded area in a closed viscus with residual urine and a considerable amount of electrocoagulated dead tissue gives a combination that may cause trouble. Major intravesical operations must be followed by complete drainage, and if it is necessary to resect large amounts of obstructing tissue, suprapubic cystostomy should first be done.

TESTIS, EPIDIDYMIS AND SEMINAL VESICLES

Undescended Testis.—Wangensteen [45] stated that the imperfectly descended testis is aspermatic because of its position. Before puberty the undescended testis is not unlike one in the scrotum. The scrotum serves as a thermoregulating mechanism, and a scrotal testis is normal in the adult only. The undescended testis is more likely to become

44. Bumpus, H. C., Jr.: Transurethral Resection of the Prostate Gland, Proc. Staff Meet., Mayo Clin. **7**:249 (April 27) 1932.

45. Wangensteen, O. H.: The Surgery of the Undescended Testis, Surg., Gynec. & Obst. **54**:219 (Feb.) 1932.

malignant than the normally descended one, and scrotal fixation does not diminish this predisposition to malignancy. The undescended testis, however, is not a precarcinomatous lesion, and malignant lesions of the testis are rare.

The treatment of undescended testis is placing the organ in the scrotum without injury to the testicular blood vessels. There should be adequate mobilization of the vessels of the testis for the success of the procedure. Temporary adequate scrotal anchorage should be a part of the technic; without it, retraction occurs and the testis does not grow to normal size. The best time to perform the operation of orchiopexy is when the patient is between 8 and 11 years old; to insure good functional result the operation should be done before puberty.

[COMPILERS' NOTE.—The work of Torek and Bevan on the undescended testis has been a distinct contribution to American urology. The principles of free mobilization of the spermatic cord with maintenance of testicular blood supply, together with fixation of the testis by some form of temporary or permanent anchorage in the scrotum, are well known. Retraction of the testis, as Wangensteen observed, is a frequent cause of failure and must be carefully guarded against; this is done by his procedure of temporary anchorage to the thigh. It is generally agreed that the operation offers best results if done between the ages of 8 and 11 years.]

Hepler [46] summarized the generally accepted conclusions on undescended testes as follows: The testis before puberty, in its normal position, and the undescended testis before puberty are grossly and histologically similar. The apparent atrophy of the undescended testis before puberty does not indicate that it should be disregarded or removed because it is of no value; under proper environment it is potentially a normal testis. The undescended testis of adults is aspermatic because of degeneration of the germinal epithelium, which is attributable to the constantly higher temperature to which the testis is exposed when retained in the abdomen or inguinal region than when it is afforded protection by the scrotum. If the undescended testis is properly placed in the scrotum before puberty, spermatogenesis will later take place and it will develop normally. The best age for orchiopexy is between the ages of 6 and 10 years. The testis should not be replaced before the fifth year unless there is some complication which needs correction. A normally functioning organ should not be expected if replacement is delayed too long after puberty, although the cosmetic effect may be satisfactory.

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46. Hepler, A. B.: Surgery of the Undescended Testes: A Modified Torek Operation, West. J. Surg. **40**:286 (June) 1932.

The essential features of successful orchiopexy are careful and complete separation of the component structures of the spermatic cord without interference with the blood supply of the testis, and the temporary fixation of the testis to some structure outside the scrotum to prevent retraction until this tendency has been overcome. A modification of the Torek operation is described, which has given satisfactory results in 12 cases in the last year. This technic, or some modification of it, has been increasingly popular and has given complete satisfaction because the late results are as good as the early results.

Walters [8] stated that the operation of Torek and Meyer is being used more often for cases of cryptorchidism than formerly. As much length as possible is added to the cord by separation of the hernial sac and division of connective tissue joining the spermatic vessels and the vas deferens. The testis is then brought down into and through an incision in the scrotum and attached to the fascia lata of the thigh. After four weeks, the testis is dissected from the fascia lata of the thigh and the skin of the scrotum from the skin of the thigh, the testis is replaced in the scrotum and both incisions are then closed. In 200 operations on the testis and epididymis, 48 plastic operations were performed for undescended testis, in practically all of which the principle described by Torek was employed. There was no mortality. In approximately 100 cases of cryptorchidism in which this operation has been performed in the last five years, the results have been uniformly successful, and the field of applicability of the operation has been extended to include even cases of intra-abdominal testis. In only 3 cases of undescended testis last year was orchidectomy necessary.

Carcinoma of the Testis.—Chevassu [47] considered the procedure to be followed when carcinoma of the testis is suspected. A significant point in the diagnosis is the presence of a hard area in a testis apparently normal otherwise. This should be immediately confirmed by exploration with the patient under local anesthesia, at which time unusual vascularization of the albuginea would suggest malignancy. There should be no hesitation in performing exploratory orchotomy when the diagnosis is doubtful.

Toulson [48] stated that inflammatory masses occurring chronically in and about the testis may undergo hyalinization and lead to a mistaken diagnosis of new growth. Hyalin is rather commonly observed in the pleura, pericardium and spleen, but is rare in the testis. Hyalinization of a hydrocele is a state in the chronic process of the inflammation, and tends to undergo calcification.

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47. Chevassu, Maurice: Diagnostic immédiat et précoce des cancers du testicule, Bull. et mém. Soc. nat. de chir. **58**:475 (March 19) 1932.

48. Toulson, W. H.: The Hyalinization of Hydrocele Sacs, J. Urol. **28**:247 (Aug.) 1932.

Carcinoma of the Epididymis.—Coleman, Mackie and Simpson[49] reported the clinical and pathologic findings in a case of primary malignant teratoma (embryonal carcinoma) of the epididymis. The neoplasm corresponded structurally to the most common form of malignant neoplasm originating in the testis. The evidence appears to be conclusive that these neoplasms have their origin in preexisting teratomas, in which one of the tissue elements undergoes malignant transformation. Removal of the testis, epididymis and spermatic cord is usually of no benefit in view of the fact that metastasis occurs relatively early in these cases.

[COMPILERS' NOTE.—Malignant tumors of the epididymis are extremely rare, only a small number having been reported in the literature. In the small series of case histories reported, these tumors are as rapidly fatal as those of teratoma of the testis. A few cases of benign tumors of the epididymis have also been reported; recently Hinman and Gibson reviewed 10 cases of sarcoma from the literature. A few angiomas of the epididymis have also been described.]

PENIS

Hypospadias.—Hagner[50] stated that incurvation of the penis in hypospadias is caused by the shortening of the fibrous tissue which, in this malformation, replaces the corpus spongiosum. A method of grafting skin for this condition is reported. The graft, including all the layers of the skin, is cut from the inner side of the thigh and placed in saline solution. A cannula is then thrust through the corpora cavernosa, care being taken to place it above the line of the fibrous tissue that causes the chordee. The cannula is then withdrawn; the skin graft is placed around it, the skin side next to the instrument, and two or three fine catgut sutures are used to bring the edges together. The cannula is reintroduced through the puncture and the graft is slipped off, two fine catgut sutures being placed at the ends to hold it in position. Two of these grafts are usually sufficient. The urine is drained by a retention catheter in the opening of the perineal or the scrotal urethra, and a sterile dressing is then applied. The grafts heal rapidly. At the end of two or three weeks a grooved director is passed through the graft and incised from within outward to the surface of the skin. The graft tends to flatten out as soon as the incision is made; after a month or six weeks the grafted area

49. Coleman, C. A.; Mackie, J. A., and Simpson, W. M.: Primary Malignant Neoplasms of the Epididymis, Surg., Gynec. & Obst. **55**:111 (July) 1932.

50. Hagner, F. R.: A New Method for Straightening the Penis in Hypospadias, J. A. M. A. **99**:116 (July 9) 1932.

can be noticed only by the difference in the appearance of the skin, while palpation at the base of the graft discloses no tendency to the formation of scar tissue.

Cecil [51] stated that in the surgical treatment of hypospadias a good result cannot be obtained without complete diversion of the urinary stream; this is brought about by occlusion of the urethra by suture. Drainage tubes, probes and other foreign bodies should not be left in the newly formed urethra. The primary operation for correction of the deformity of the penis should be done in the first two years of life. It should be complete, and no other operation should be done until it has been proved that the deformity has been cured.

Heteroplastic grafts are of no value for reconstruction of the urethra. Autoplastic free grafts, such as the use of the appendix, veins, arteries or free skin grafts, after the method of Nove-Josserand, are unsatisfactory in reconstructing the urethra. The most successful method is by the technic of Thiersch, which is applicable to all forms of hypospadias.

Epispadias with incontinence is curable in many cases. Transplantation of the ureters to the bowel should be done only in cases in which it has been impossible to reconstruct the vesical neck. The most desirable method of reconstructing the neck of the bladder and urethra is the method proposed by Young, which was described fully by Cecil.

[COMPILERS' NOTE.—Diversion of the urinary stream as an initial procedure in the surgical treatment of hypospadias is well established. Cecil's avoidance of a drainage tube or probe to splint the newly formed urethra is noteworthy. Many plastic procedures have been described to fulfil the requirements presented by the individual case. Perhaps the technic of DuPlay or one of its modifications is most often used. The technic of Van Hacker or Beck tends to constrict the penis or to increase its curvature to definite disadvantage. A preputial skin flap to form a new channel has been successfully used by Mayo and by Young. When autografts are used, the latter author prefers whole thickness grafts from the thigh.]

Carcinoma.—Leighton [52] contributed a summary of 67 cases of carcinoma of the penis. Of 24 patients who did not receive treatment, 3 died of carcinoma and 1 of an unknown cause; 19 have not been traced and 1 was operated on elsewhere. Of 43 patients who were treated, 4 had roentgen or radium therapy. Three of these died and 1 could not be traced.

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51. Cecil, A. B.: Surgery of Hypospadias and Epispadias in the Male, West. J. Surg. **40**:297 (June) 1932.

52. Leighton, W. E.: Carcinoma of the Penis, with a Report of Sixty-Seven Cases, Am. J. Cancer **16**:251 (March) 1932.

Various surgical procedures were performed in 34 cases. Partial amputation of the penis was done in 3 cases, partial amputation with inguinal dissection in 5, total amputation in 1 case, total amputation with inguinal dissection in 11 cases and total emasculation in 14. Five of the 34 patients operated on have not been traced. Fourteen died, 2 after operation and 3 of recurrence; 9 lived from one month to eighteen years, death being due to causes other than carcinoma. Nineteen are living from six months to twenty-five years after operation.

According to Broders' classification of malignancy, 5 carcinomas were graded 1; 19 carcinomas, 2; 6 carcinomas, 3, and 1 carcinoma, 4. In each of the 3 cases in which death resulted from recurrence there was metastasis in the inguinal lymph nodes at operation. Five patients who had tumors graded 2 with inguinal metastasis at the time of operation are still alive and free from recurrence.

[COMPILERS' NOTE.—Carcinoma of the penis, papillary or flat usually arises beneath a tight redundant prepuce. The prophylactic procedure of circumcision in youth cannot be too greatly emphasized. Advocates of radical surgery, such as the procedure outlined by Young, and of roentgen therapy vie with one another as to the excellence of end-results. Increasing evidence shows the superiority of radium treatment if applied early and before the invasion of Buck's fascia. Here again the prognostic importance of the grade of malignancy in determining the probability of cure or of length of life after any form of treatment is noteworthy.]

URETHRA

Tumors.—Kirwin [53] stated that the most common type of epithelioma of the urethra is squamous cell carcinoma; the papillary form occurs less frequently and the columnar cell type rarely. One adenocarcinoma is recorded in the literature. In cases in which the exact site of origin was ascertainable, the growth appeared most often in the perineal or membranous portion of the urethra. The fact that squamous cell carcinoma arises in these portions of the urethra is accounted for by some writers as due either to metaplasia or to embryonal inclusion in the cell nest. There may be formation of patches of leukoplakia which later undergo malignant degeneration. The continuous passage of infected, irritating urine over a surface already injured by inflammation and the passage of instruments would inevitably produce a hyperplastic reaction. In at least two thirds of the cases reported in the literature there was a previous history of stricture, sometimes for as long as thirty years, before malignancy became evident.

53. Kirwin, T. J.: Primary Epithelioma of the Urethra, J. Urol. **27**:539 (May 1932.

Gonorrhea is apparently an important factor in the production of urethral carcinoma, owing to the frequency of stricture as an antecedent to the lesion. Chronic urethritis would seem likely to produce the conditions under which malignancy would develop rapidly. In some cases there was a history of the previous removal of benign papillomas. In 1 case there had been infection urethritis, and for twenty years it had been necessary to dilate the resulting stricture frequently. Guyon cited a case of urethral carcinoma in which there were multiple fistulas after urethritis of long standing, and Englisch reported a case of periurethral abscess with formation of fistula and development of a malignant lesion after three years' continuous drainage.

Difficulty in urination is the chief complaint. The urinary stream diminishes in size and volume until it is reduced to a mere dribble, and even then straining is necessary to effect partial evacuation of the bladder. Palpation usually reveals one or more hard nodules.

Kirwin reported a case in which the original lesion, close to the urinary meatus, was excised with the bipolar cautery, the metastatic inguinal nodes were removed and the inguinal wounds were treated, first by implantation of radon and later by Alpine light and deep roentgen rays. Examination after four months disclosed slight recurrence, but this was controlled by further cauterization. The patient is still in good condition.

Mercier [54] reported a case of carcinoma of the urethra of a man, aged 59. At the age of 19 years he had had urethritis, leaving contractions of the canal, which had been dilated several times. At examination only a filiform bougie could be passed into the urethra. Pus and bacteria in the urine suggested an abscess of the urinary tract. Internal urethrotomy was performed, and the abscess was drained of thick, foul pus. Convalescence was uneventful for about a month; at that time a perineal fistula was noted. The urethra admitted only a no. 24 bougie. Urethrotomy was performed again, and the fistula was widely opened. A granular mass in the bulbar portion of the urethra led to a diagnosis of squamous cell epithelioma. Resection was performed, followed by treatment with radium.

Carcinoma of the urethra in the male is rare, and is usually situated in the region of the corpora cavernosa. It is seldom correctly diagnosed at the onset of symptoms because the patients do not seek treatment until marked dysuria and pollakiuria are present or sometimes until a perineal urinary fistula has formed. Urethrorrhagia is not an early symptom. The objective symptom most often noted is a perineal or penile tumor without accompanying pain. Urethroscopy or operation is

54. Mercier, Oscar: Un cas de cancer de l'urètre chez l'homme, Union méd. du Canada **61**:336 (Feb.) 1932.

necessary to determine the diagnosis. The significant facts in this case were that an epithelioma had developed on an old stricture and that, after dilatation and urethrotomy, the stricture formed again with unusual rapidity. It is emphasized that any stricture of the urethra which does not respond to suitable treatment should be suspected of being produced by an epithelioma.

[COMPILERS' NOTE.—These pathologic lesions of the urethra, although rare, must be borne in mind, and in some instances in which there is a history of a stricture of the urethra or of other lesions which have recurred, it is important that the preoperative diagnosis be as accurate as possible. When the diagnosis is not clinically established, urethrography should be done. Gutierrez and Lowsley,[55] when reporting 6 cases of diverticulum of the urethra, found in the literature 116 cases, in most of which the diagnosis was made at operation and in many instances was followed by perineal and urethral complications for lack of correct diagnosis. The study revealed the importance of taking urethrograms in all unrecognized pathologic conditions of the urethra. This applies to primary malignant growth of the urethra and the so-called incurable cases of multiple stricture of the urethra.]

UROGRAPHY

Mark and Johnson[56] stated that 25 per cent sodium bromide is unsuitable and dangerous as a urographic medium because of the constant injury to the mucosa of the bladder, even when no undue pressure or overdistention is present, and because its action is markedly hemolytic. Sodium iodide in 12.5 per cent solution, although causing much less hemolysis than sodium bromide, produces a recognizable edema of the mucosa and irritation. Iopax in 30 per cent solution causes approximately the same degree of hemolysis as 12.5 per cent sodium iodide, but its use is unaccompanied by any mucosal or submucosal change, and there is no evidence of irritation. Skiodan (methiodal) in 20 per cent solution causes no hemolysis and is totally free from any irritating qualities.

The use of either iopax or skiodan (methiodal) eliminates the danger of bilateral pyelograms when they are necessary for renal and ureteral study. Overdistention is productive of injury and pain, even if mild solutions are used, but the real factor in causing irritation and

55. Gutierrez, R., and Lowsley, O. S.: Chirurgische Behandlung der Harnröhrendivertikel mit Projektion, Verhandl. d. deutsch. Gesellsch. f. Urol. **8**:312, 1928.

56. Mark, E. G., and Johnson, E. T.: The Immediate Effects of Various Pyelographic Media upon the Mucosa, J. Urol. **27**:595 (May) 1932.

injury to mucosa is in the character of the drug itself and its immediate effects on the mucosa.

Wesson [57] compared the relative merits of iopax, skiodan (methiodal), and neo-iopax for intravenous urography. Neo-iopax was the most satisfactory because of the sharpness of pictures, absence of untoward reactions and ease of administration. The best neo-iopax pictures were usually made at five minutes. In cases in which rupture of a kidney, ureter or bladder is suspected, intravenous urography should be the first diagnostic procedure. In acute cases of ureteral stone the urogram on the unaffected side will be good and will show an increased density of the kidney on the affected side, but no outline or a delayed outline of the pelvis and ureter will be observed.

Intravenous urography is only one of the various diagnostic procedures, and its findings should be checked as far as possible by retrograde cystoscopy. To a certain extent it has restored a large field of medicine to the general practitioner, but the ultimate exact diagnosis should depend on the more conclusive data of the urologist.

Dourmashkin [58] stated that intravenous pyelography frequently supplies the only medium for ascertaining renal function on the affected side when there is apparently complete obstruction of the ureter by calculus. In the majority of chronic cases of ureteral stone, intravenous pyelography demonstrated perfect renal drainage. The presence of impassible obstruction is not a criterion which determines complete impaction, for in many such cases perfect drainage is revealed by intravenous pyelography. This method is of no aid in localizing calculi composed of uric acid. Open operation should not be used in any case unless its indications are clearly defined by intravenous pyelography.

URINARY ANTISEPTICS

Riaboff [59] stated that pyridium is eliminated in high concentration by the kidneys of normal subjects. If patients are in bed its elimination is considerably lower than normal. When administered by mouth it is not toxic or irritating to the genito-urinary tract. A pathologic study of organs removed from animals given pyridium in large doses disclosed no destructive or degenerative processes in the tissues. It had some bactericidal and bacteriostatic effects on Bacillus coli and

57. Wesson, M. B.: Intravenous Urography: A New Diagnostic Procedure for the General Practitioner, Urol. & Cutan. Rev. **36**:296 (May) 1932.

58. Dourmashkin, R. L.: The Value of Intravenous Pyelography in the Management of Ureteral Calculi: Based on a Study of 45 Cases, J. Urol. **27**:637 (June) 1932.

59. Riaboff, P. J.: A Study of Pyridium as a Urinary Antiseptic with Special Reference to Its Elimination by the Kidneys, J. Urol. **27**:329 (March) 1932.

Staphylococcus aureus in water and urine. Pyridium excreted in the urine had no bactericidal or bacteriostatic effects on Bacillus coli or Staphylococcus aureus in vitro.

UROLOGY AND GYNECOLOGY

Stevens [60] expressed the opinion that the urologist should have some knowledge of gynecology and be conversant with the pathologic conditions of the abdomen and pelvis. Because of the frequent similarity of symptoms and not uncommon association of lesions of the female urinary and generative organs, examinations of both tracts is almost always indicated, particularly before surgical procedures. Vaginal examination will reveal many of the lesions of the urethra, bladder and lower third of the ureters, as well as those of the uterus, tubes, ovaries and broad ligaments. Study of 1,052 female patients with symptoms relating to the urinary tract disclosed that pathologic or physiologic conditions of the generative organs were possible or probable etiologic factors in about 25 per cent. Salpingitis is the most common pelvic condition requiring to be distinguished from disease of the urinary tract.

Injuries to the bladder and especially to the ureters during gynecologic operations are not unusual. Partial or complete retention of urine is common, and occasionally, pyelonephritis, as a postoperative complication in the majority of cases. The urethra should be thoroughly examined, since pathologic conditions are more common in this organ than in any other portion of the urinary tract. Such conditions often are responsible for symptoms suggestive of lesions of the generative organs of women. Infections and other pathologic changes of the adnexa should be eradicated in the treatment of many urologic lesions.

[COMPILERS' NOTE.—It is remarkable that gynecology and urology have been separated as specialties, since the former implies a study of the generative part of the genito-urinary system of women. No such division in practice has been made in the case of men. The Kelly school in Baltimore has long held that the two fields should be included under one specialty. Certainly the proximity of the urinary and the generative system in women and the frequency of associated disease make it imperative that the gynecologic specialist be familiar with urology, and vice versa. Stevens' presentation offers a good argument in favor of this contention.]

60. Stevens, W. E.: Differential Diagnosis of Pathologic Conditions of the Urinary Tract and the Female Generative Organs, J. Urol. **27**:103 (Jan.) 1932.